```
=> d his

     (FILE 'REGISTRY' ENTERED AT 14:16:55 ON 05 FEB 2004)
                DEL HIS Y
L1            3 S 9002-93-1 OR 9002-92-0 OR 9005-65-6
                E TRITON/CN
L2            1 S E6
                E TWEEN/CN

     FILE 'CAPLUS' ENTERED AT 14:19:09 ON 05 FEB 2004
L3        38871 S L1 OR L2 OR TWEEN OR TRITON
L4        36722 S VACCINE?/CW
L5        12706 S INFLUENZA (L) VIRUS
L6           39 S L3 AND L4 AND L5
L7        59758 S SPLIT OR SPLIT/AB
L8            6 S L6 AND L7
L9       101929 S SURFACTANTS?/CW
L10          32 S L4 AND L9 AND L5
L11           3 S L7 AND L10
L12           6 S L11 OR L8

     FILE 'WPIDS' ENTERED AT 14:23:52 ON 05 FEB 2004
L13        2528 S TRITON OR TWEEN  OR OCTYLPHENOXYPOLYETHOXYETHAN?
L14        1195 S INFLUENZ? (S) VACCIN?
L15          17 S L13 AND L14
L16       93731 S SURFACTANT?
L17          47 S L14 AND L16
L18          55 S L15 OR L17
L19       72375 S SPLIT
L20          10 S L19 AND L18

     FILE 'WPIDS, CAPLUS' ENTERED AT 14:25:35 ON 05 FEB 2004
L21          12 DUP REM L20 L12 (4 DUPLICATES REMOVED)
```

```
=> fil reg
FILE 'REGISTRY' ENTERED AT 14:49:24 ON 05 FEB 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2004 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:     4 FEB 2004  HIGHEST RN 646450-50-2
DICTIONARY FILE UPDATES:    4 FEB 2004  HIGHEST RN 646450-50-2

TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2003

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=> d que l1
L1             3 SEA FILE=REGISTRY ABB=ON  PLU=ON  9002-93-1 OR 9002-92-0 OR
                 9005-65-6


=> d l1 rn cn 1-3

L1   ANSWER 1 OF 3  REGISTRY  COPYRIGHT 2004 ACS on STN
RN   9005-65-6  REGISTRY
CN   Sorbitan, mono-(9Z)-9-octadecenoate, poly(oxy-1,2-ethanediyl) derivs.
     (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   Glycols, polyethylene, ether with sorbitan monooleate (8CI)
OTHER NAMES:
CN   Alkamuls PSMO 20
CN   Alkamuls T 80
CN   Atlox 1087
CN   Atlox 8916TF
CN   Capmul POE-O
CN   Cemerol T 80
CN   Cemesol TW 1020
CN   Crill 10
CN   Crill 11
CN   Crill S 10
CN   Crillet 4
CN   Crillet 4 Super
CN   Crillet 41
CN   Disponil SMO 120
CN   Durfax 80
CN   E 433
CN   Ecoteric T 80
CN   Emasol O 105R
CN   Emsorb 6900
CN   Emulson 10OM
CN   Ethoxylated sorbitan monooleate
```

CN Ethylene oxide-sorbitan monooleate polymer
CN Eumulgin SMO 20
CN Flo Mo SMO 20
CN Glycosperse O 20
CN Glycosperse O 5
CN Hexaethylene glycol sorbitan monooleate
CN Hodag SVO 9
CN Ionet T 80
CN Ionet T 80C
CN Lamesorb SMO 20
CN MO 55F
CN Montanox 80
CN Montanox 81VG
CN Montanox DF 80
CN Myvatex MSPS
CN Nikkol TO 10
CN Nikkol TO 106
CN Nikkol TO 10M
CN Nissan Nonion OT 221
CN Nonio-light 0-30
CN Nonio-light SPO 1
CN Nonion OT 221
CN Olothorb
CN POE sorbitan monooleate
CN Polisorbac 60
CN Polyethoxylated sorbitan monooleate
CN Polyethylene glycol sorbitan ether monooleate
CN Polyethylene glycol sorbitan monooleate
ADDITIONAL NAMES NOT AVAILABLE IN THIS FORMAT - Use FCN, FIDE, or ALL for DISPLAY

L1 ANSWER 2 OF 3 REGISTRY COPYRIGHT 2004 ACS on STN
RN **9002-93-1** REGISTRY
CN Poly(oxy-1,2-ethanediyl), α-[4-(1,1,3,3-tetramethylbutyl)phenyl]-ω-hydroxy- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Glycols, polyethylene, mono[p-(1,1,3,3-tetramethylbutyl)phenyl] ether (8CI)
CN Phenol, p-(1,1,3,3-tetramethylbutyl)-, monoether with polyethylene glycol (8CI)
OTHER NAMES:
CN (p-t-Octylphenoxy)polyethoxyethanol
CN α-[p-(1,1,3,3-Tetramethylbutyl)phenyl]-ω-hydroxypoly(oxyethylene)
CN Anapoe X 114
CN Antarox A 200
CN Hydrol SW
CN Iconol OP
CN Koromex II
CN NOP 90
CN OPE 30
CN Ortho-Gynol
CN p-tert-Octylphenoxy polyethoxyethanol
CN Photo-Flow 200
CN Poly(oxyethylene) p-tert-octylphenyl ether
CN Polyethylene glycol mono(4-octylphenyl) ether
CN Polyethylene glycol mono(4-tert-octylphenyl) ether
CN Polyethylene glycol mono(p-tert-octylphenyl) ether
CN Polyethylene glycol mono[p-(1,1,3,3-tetramethylbutyl)phenyl] ether
CN Polyethylene glycol p-(1,1,3,3-tetramethylbutyl)phenyl ether

CN Polyethylene glycol p-octylphenyl ether
CN Polyethylene glycol p-tert-octylphenol ether
CN Polyethylene glycol p-tert-octylphenyl ether
CN Polyethylene oxide-p-tert-octylphenyl ether
CN Polyoxyethylene (13) octylphenyl ether
CN Polyoxyethylene (9) octylphenyl ether
CN Polyoxyethylene glycol-p-tert-octylphenyl ether
CN Polyoxyethylene mono(octylphenyl) ether
CN Preceptin
CN Texofor FP 300
CN Triton X 100
CN Triton X 101
CN Triton X 102
CN Triton X 114
CN Triton X 15
CN Triton X 165
CN Triton X 305
CN Triton X 35
CN Triton X 405
CN Triton X 45
CN Triton X 705
CN Triton X 705-70
CN TX 100
CN TX 102
CN TX 305
CN TX 405

L1 ANSWER 3 OF 3 REGISTRY COPYRIGHT 2004 ACS on STN
RN **9002-92-0** REGISTRY
CN Poly(oxy-1,2-ethanediyl), α-dodecyl-ω-hydroxy- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN α-Dodecyl-ω-hydroxypoly(oxy-1,2-ethanediyl)
CN α-Dodecyl-ω-hydroxypoly(oxyethylene)
CN 40L
CN 40L (polyether)
CN Actinol L 3
CN Actinol L 7
CN Adeka Carpol MBF 100
CN Adekatol LA 1275
CN Adekatol LA 50
CN Aethoxysklerol
CN Aetoxisclerol
CN Akyporox RLM 160
CN Akyporox RLM 22
CN Akyporox RLM 230
CN Akyporox RLM 40
CN Aldosperse L 9
CN Alkasurf LAN 1
CN Alkasurf LAN 3
CN Arapol 0712
CN Atlas G 2133
CN Atlas G 3705
CN Atlas G 3707
CN Atlas G 4829
CN Atmer 135
CN B 205
CN Base LP 12
CN BL 2
CN BL 9

CN BL 9 (polyglycol)
CN BL 9EX
CN Blaunon EL 1503P
CN Blaunon EL 1509
CN Brij 22
CN Brij 23
CN Brij 30
CN Brij 30ICI
CN Brij 30SP
CN Brij 35
CN Brij 35L
CN Brij 35P
CN Brij 36T
CN Calgene 40L
CN Carsonol L 2
CN Carsonol L 3
CN Chemal LA 23
CN Chemal LA 4
CN Chimipal AE 3
CN Cimagel
CN Conion 275-100
CN Conion 275-20
ADDITIONAL NAMES NOT AVAILABLE IN THIS FORMAT - Use FCN, FIDE, or ALL for DISPLAY

=> d que l2

L2 1 SEA FILE=REGISTRY ABB=ON PLU=ON "TRITON (SURFACTANT)"/CN

=> d l2

L2 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2004 ACS on STN
RN 9083-53-8 REGISTRY
CN **Triton (surfactant) (9CI)** (CA INDEX NAME)
OTHER NAMES:
CN Triton
MF Unspecified
CI PMS, COM, MAN
PCT Manual registration
LC STN Files: ANABSTR, BIOSIS, CA, CAPLUS, CASREACT, IFICDB, IFIPAT, IFIUDB, NIOSHTIC, PDLCOM*, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
176 REFERENCES IN FILE CA (1907 TO DATE)
5 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
176 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> fil wpids caplus
FILE 'WPIDS' ENTERED AT 14:50:07 ON 05 FEB 2004
COPYRIGHT (C) 2004 THOMSON DERWENT

FILE 'CAPLUS' ENTERED AT 14:50:07 ON 05 FEB 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)

```
=> d que l21
L1             3 SEA FILE=REGISTRY ABB=ON  PLU=ON  9002-93-1 OR 9002-92-0 OR
                 9005-65-6
L2             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "TRITON (SURFACTANT)"/CN
L3         38871 SEA FILE=CAPLUS ABB=ON  PLU=ON  L1 OR L2 OR TWEEN/OBI OR
                 TRITON/OBI
L4         36722 SEA FILE=CAPLUS ABB=ON  PLU=ON  VACCINE?/CW
L5         12706 SEA FILE=CAPLUS ABB=ON  PLU=ON  INFLUENZA/OBI (L) VIRUS/OBI
L6            39 SEA FILE=CAPLUS ABB=ON  PLU=ON  L3 AND L4 AND L5
L7         59758 SEA FILE=CAPLUS ABB=ON  PLU=ON  SPLIT/OBI OR SPLIT/AB
L8             6 SEA FILE=CAPLUS ABB=ON  PLU=ON  L6 AND L7
L9        101929 SEA FILE=CAPLUS ABB=ON  PLU=ON  SURFACTANTS?/CW
L10           32 SEA FILE=CAPLUS ABB=ON  PLU=ON  L4 AND L9 AND L5
L11            3 SEA FILE=CAPLUS ABB=ON  PLU=ON  L7 AND L10
L12            6 SEA FILE=CAPLUS ABB=ON  PLU=ON  L11 OR L8
L13         2528 SEA FILE=WPIDS ABB=ON  PLU=ON  TRITON OR TWEEN  OR OCTYLPHENOXY
                 POLYETHOXYETHAN?
L14         1195 SEA FILE=WPIDS ABB=ON  PLU=ON  INFLUENZ? (S) VACCIN?
L15           17 SEA FILE=WPIDS ABB=ON  PLU=ON  L13 AND L14
L16        93731 SEA FILE=WPIDS ABB=ON  PLU=ON  SURFACTANT?
L17           47 SEA FILE=WPIDS ABB=ON  PLU=ON  L14 AND L16
L18           55 SEA FILE=WPIDS ABB=ON  PLU=ON  L15 OR L17
L19        72375 SEA FILE=WPIDS ABB=ON  PLU=ON  SPLIT
L20           10 SEA FILE=WPIDS ABB=ON  PLU=ON  L19 AND L18
L21           12 DUP REM L20 L12 (4 DUPLICATES REMOVED)


=> d bib abs it tech l21 1-12

L21  ANSWER 1 OF 12  WPIDS  COPYRIGHT 2004 THOMSON DERWENT on STN DUPLICATE 1
AN   2003-120370 [11]   WPIDS
DNC  C2003-030969
TI   Use of trivalent, non-live influenza antigen preparations in the
     manufacture of a 1-dose influenza vaccine for
     intradermal delivery.
DC   A25 A96 B04 D16
IN   GARCON, N; SLAOUI, M M; VAN HOECKE, C
PA   (GLAX) GLAXOSMITHKLINE BIOLOGICALS SA; (SMIK) SMITHKLINE BEECHAM
     BIOLOGICALS
CYC  101
PI   WO 2002074336 A2 20020926 (200311)* EN   51p
        RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ
            NL OA PT SD SE SL SZ TR TZ UG ZM ZW
         W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
            DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
            KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT
            RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM
            ZW.
     EP 1361890    A2 20031119 (200377)  EN
         R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT
            RO SE SI TR
ADT  WO 2002074336 A2 WO 2002-EP1844 20020221; EP 1361890 A2 EP 2002-724176
     20020221, WO 2002-EP1844 20020221
FDT  EP 1361890 A2 Based on WO 2002074336
PRAI GB 2001-8365     20010403; GB 2001-4538     20010223; GB 2001-7511
     20010326
AN   2003-120370 [11]   WPIDS
AB   WO 200274336 A UPAB: 20030214
     NOVELTY - The use of a trivalent non-live influenza antigen
     preparation in the manufacture of one-dose influenza
```

vaccine for intradermal delivery, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for following:

(1) preparation of an influenza antigen formulation involving:

(a) harvesting of virus-containing material from a culture;

(b) clarification of the harvested material to remove non-virus material;

(c) concentration of harvested virus; separating whole virus from non-virus material;

(d) splitting the whole virus using a splitting agent in a density gradient centrifugation; and

(e) filtering the undesired materials; and

(2) a kit comprising an intradermal delivery device and the trivalent non-live **influenza vaccine.**

ACTIVITY - Virucide.

MECHANISM OF ACTION - Vaccine.

100 Male and females volunteers were enrolled and randomized in 2 groups. The vaccine was administered by two routes. The vaccine was supplied as a pre-filled syringe for intramuscular (IM) injection in deltoid region of the non-predominant arm. The vaccine was supplied as 0.5 ml of ampoule dose. 0.2 of the full dose (100 micro l) was injected intradermally (ID) using a device as disclosed in EP1092444. The duration of the study was approx. 21 days per subject with only one dose of vaccine given intramuscularly or intradermally. Blood was sampled at day 0 - 21. The conversion factor (fold increase in serum HI the geometric mean titres (GMT)s on day 21 compared to day 0) for group Fluarix (RTM) (IM)/ Fluarix (RTM) (ID) were 10.6/9.1, 9.3/9.2, and 10.9/8.5 for antigen A/N-Caledonia, A/Panama and B/Yamanashi respectively.

USE - For the preparation of flu **vaccine** for intradermal delivery (claimed) for treating respiratory disease and **influenza** complications.

ADVANTAGE - The intradermal administration of the low antigen dose vaccine can produce a systemic seroconversion (4-fold increase in anti-HA titres) equivalent to that obtained by subcutaneous administration of the same vaccine. The vaccine is administered in a single dose and it stimulates systemic immunity at a protective level with a low dose of antigen.

Dwg.0/1

TECH UPTX: 20030214

TECHNOLOGY FOCUS - BIOLOGY - Preferred **Vaccine**: The **vaccine** further comprises at least one non-ionic **surfactant** selected from octyl- or nonylphenoxy polyoxyethanols (e.g. **Triton** (RTM) series), polyoxyethylene sorbitan esters (e.g. **Tween** (RTM) series), polyoxyethylene ethers and/or esters of formula (I) (preferably a combination of polyoxyethylene sorbitan monooleate (**Tween** 80 (RMT)) and t-octylphenoxy polyethoxyethanol (**Triton** X-100 (RTM)).

$HO(CH_2CH_2O)n-A-R$ (I)

n = 1 - 50;

A = bond or -C(O)-;

R = 1-50C alkyl, or phenyl(1-50C)alkyl.

The **vaccine** further comprise a bile acid or cholic acid, or their derivatives such as sodium deoxy cholate. The **vaccine** comprises the antigen dose of 1 - 7.5 micrograms haemagglutinin per stain of **influenza.** The **vaccine** additionally comprises an adjuvant comprising a combination of cholesterol, a saponin and an LPS derivative.

Preferred Antigen: The antigen preparation is a **split influenza** preparation. The **influenza** antigen is egg derived.

Preferred Kit: The intradermal delivery device is a short needle device.

The kit comprises 0.05 - 0.2 ml of **vaccine.**

L21 ANSWER 2 OF 12 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN DUPLICATE 2
AN 2002-713478 [77] WPIDS
DNC C2002-202312
TI IVX-908 adjuvant composition comprising an outer membrane protein proteosome preparation and liposaccharide preparation, useful in preparing immunogenic composition, vaccines or immunotherapeutics against cancer or allergies.
DC B04 D16
IN BURT, D S; JONES, D; LOWELL, G H; RIOUX, C; WHITE, G L
PA (BURT-I) BURT D S; (JONE-I) JONES D; (LOWE-I) LOWELL G H; (RIOU-I) RIOUX C; (WHIT-I) WHITE G L; (INTE-N) INTELLIVAX INT INC
CYC 100
PI WO 2002072012 A2 20020919 (200277)* EN 50p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW
US 2003044425 A1 20030306 (200320)
ADT WO 2002072012 A2 WO 2002-US7108 20020311; US 2003044425 A1 Provisional US 2001-274232P 20010309, Provisional US 2001-327297P 20011009, US 2002-94424 20020311
PRAI US 2001-327297P 20011009; US 2001-274232P 20010309; US 2002-94424 20020311
AN 2002-713478 [77] WPIDS
AB WO 200272012 A UPAB: 20021129
NOVELTY - An adjuvant composition, IVX-908, comprising an outer membrane protein proteosome preparation prepared from a first gram-negative bacteria, and a liposaccharide preparation derived from a second gram-negative bacteria, is new.

DETAILED DESCRIPTION - An adjuvant composition, IVX-908, comprising an outer membrane protein proteosome preparation prepared from a first gram-negative bacteria, and a liposaccharide preparation derived from a second gram-negative bacteria, is new. The outer membrane protein proteosome and liposaccharide preparations form a stable non-covalent adjuvant complex, where a final liposaccharide content by weight as a percentage of the total proteosome protein is at least about 13%.

INDEPENDENT CLAIMS are also included for the following:

(1) an immunogenic composition comprising the adjuvant complex cited above and an antigen;

(2) a process for preparing the adjuvant composition comprising mixing the outer protein proteosome preparation prepared from a first gram-negative bacteria, and the liposaccharide preparation derived from a second gram-negative bacteria to effect complexing of the components to form the adjuvant composition;

(3) a process for preparing an immunogenic composition comprising mixing the adjuvant complex with antigen to form the composition; and

(4) a process for inducing an immune response by administering the composition cited above to a subject.

ACTIVITY - Cytostatic; Immunosuppressive; Antiallergic.

MECHANISM OF ACTION - **Vaccine.** BALB/c mice were immunized intranasally or intramuscularly on days 1 and 21 with antigens containing 0.3-3 micro g **influenza** hemagglutinin (HA) as A/Beijing/262/95 or an A/Beijing/262/95 plus A/Sydney/5/97 bivalent detergent **split** antigen either alone or mixed with 0.3-3 micro g IVX-908 adjuvant. Control mice were given intranasal immunizations with phosphate buffered saline.

Results show that respiratory or parenteral immunization with adjuvant and **influenza split** flu antigen induces enhanced specific anti-HA antibody formation in each of the serum and mucosal samples compared to immunizing with the **influenza split** product without the adjuvant.

USE - The adjuvant complex is useful in preparing immunogenic compositions, vaccines or immunotherapeutics against cancer, autoimmune diseases or allergies. The adjuvant composition can also be used to enhance immunogenicity and improve the immune response of antigens.

Dwg.0/6

TECH UPTX: 20021129

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Adjuvant Composition: The first and second gram-negative bacteria can be the same or different. The first gram-negative bacteria is selected from genus Neisseria, preferably Neisseria meningitides. The second gram-negative bacteria is selected from Escherichia, Shigella, Plesiomonas or Salmonella, preferably Escherichia coli, Shigella flexneri, Plesiomonas shigelloides or Salmonella essens. The final liposaccharide content by weight as a percentage of the total proteosome protein is 15%-300%, 20%-200%, or 30%-150%. The proteosome preparation has a liposaccharide content about 0.5%-5%, 12%-25%, or 15%-20%. The first gram-negative bacteria is N. meningitides and the second gram-negative bacteria is S. flexneri, and the final liposaccharide content is between 50%-150%. Alternatively, the first gram-negative bacteria is N. meningitides and the second gram-negative bacteria is P. shigelloides, and the final liposaccharide content is between 50%-150%.

Preferred Immunogenic Composition: The antigen is selected from peptides, proteins, toxoids, glycoproteins, glycolipids, lipids, carbohydrates, and/or polysaccharides. The antigen is derived from a biologic or infectious organism of the animal or plant kingdom. The antigen can also be allergens or chemically or biologically modified allergens, or chemical materials. The antigen is whole or disrupted microorganisms including viruses, bacteria or parasites, attenuated and/or inactivated. The antigen is produced by synthetic or recombinant molecular procedures. The antigen is:

(a) Bet v 1a;
(b) rBet v 1a;
(c) recombinant **influenza** antigen;
(d) **influenza split** antigen;
(e) birch pollen extract; or
(f) an immunogen extract.

The immunogenic composition is a specific immunotherapeutic, adjuvanted prophylactic **vaccine** or therapeutic **vaccine.**

Preferred Process: The proteosome preparation and the liposaccharide preparation are mixed in a detergent solution, which is Empigen BB, **Triton** X-100, Mega-10. The method of (2) further comprises removing detergent by dialysis, diafiltration or ultrafiltration methodologies or their combinations. Mixing includes co-precipitation and/or lyophilization of both preparations. The method of (4), where the composition is administered by mucosal (e.g. nasal, oropharyngeal, ocular or genitourinary mucosa), enteral (e.g. oral, rectal or sublingual), parenteral (e.g. intraarterial, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, or submucosal injection or infusion), transdermal/transmucosal (topical), or inhalation (e.g. intranasal, oropharyngeal, intratracheal, intrapulmonary or transpulomonary) route to induce serum or mucosal antibodies or Type 1 cellular immune response against the antigen. The amount administered enhances an immune response. The enhanced immune response includes one or more of the following:

(a) serum IgG antibodies or serum antibodies measured in functional assays;

(b) mucosal antibodies including IgA in mucosal secretions collected from respiratory, gastrointestinal or genitourinary tracts; or
(c) correlates of cell-mediated immunity (CMI) including a shift from higher or predominant Type 2 responses to mixed, balanced, increased or predominant Type 1 responses as measured by cellular or antibody assays or Type 1 cytokine assays such as interferon gamma (IFN-gamma) with maintained, decreased or absent Type 2 cytokines such as interleukin 5 (IL-5). Administration includes a series of administration steps.

L21 ANSWER 3 OF 12 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN DUPLICATE 3
AN 2002-435301 [46] WPIDS
DNC C2002-123611
TI Vaccines comprising **split** enveloped virus preparations, useful for vaccinating against Respiratory Syncytial Virus and Parainfluenza Virus.
DC A96 B04 D16
IN COLAU, B D A; DESCHAMPS, M
PA (SMIK) SMITHKLINE BEECHAM BIOLOGICALS; (GLAX) GLAXOSMITHKLINE BIOLOGICALS SA
CYC 97
PI WO 2002028426 A1 20020411 (200246)* EN 58p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2002015914 A 20020415 (200254)
EP 1322329 A1 20030702 (200344) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
NO 2003001484 A 20030528 (200348)
CZ 2003000930 A3 20030813 (200357)
BR 2001014392 A 20030902 (200369)
KR 2003055275 A 20030702 (200377)
HU 2003002636 A2 20031128 (200405)
ADT WO 2002028426 A1 WO 2001-EP11328 20011001; AU 2002015914 A AU 2002-15914 20011001; EP 1322329 A1 EP 2001-986267 20011001, WO 2001-EP11328 20011001; NO 2003001484 A WO 2001-EP11328 20011001, NO 2003-1484 20030401; CZ 2003000930 A3 WO 2001-EP11328 20011001, CZ 2003-930 20011001; BR 2001014392 A BR 2001-14392 20011001, WO 2001-EP11328 20011001; KR 2003055275 A KR 2003-704718 20030402; HU 2003002636 A2 WO 2001-EP11328 20011001, HU 2003-2636 20011001
FDT AU 2002015914 A Based on WO 2002028426; EP 1322329 A1 Based on WO 2002028426; CZ 2003000930 A3 Based on WO 2002028426; BR 2001014392 A Based on WO 2002028426; HU 2003002636 A2 Based on WO 2002028426
PRAI GB 2001-9288 20010412; GB 2000-24088 20001002
AN 2002-435301 [46] WPIDS
AB WO 200228426 A UPAB: 20020903
NOVELTY - A vaccine formulation comprising a **split** enveloped virus preparation (the virus is Respiratory Syncytial Virus (RSV) and Parainfluenza Virus (PIV)), is new.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
(1) a method (II) of producing the vaccine formulation (I) comprising:
(a) splitting a PIV or RSV enveloped virus;
(b) optionally admixing the **split** enveloped virus preparation with a stabilizing agent; and
(c) optionally admixing the **split** enveloped virus

preparation with an adjuvant;

(2) use of a **split** RSV or PIV vaccine preparation in the manufacture of a vaccine for the prophylaxis or treatment of disease for intranasal or intradermal delivery;

(3) a kit (IV) for delivery of an intranasal vaccine formulation (I) comprising the **split** RSV or PIV enveloped virus preparation (I) and an intranasal delivery device; and

(4) a method (V) for protecting or treating a mammal susceptible to, or suffering from disease caused by PIV or RSV, comprising administering (I).

ACTIVITY - Virucide.

No suitable biological data given.

MECHANISM OF ACTION - Vaccine.

USE - The vaccine formulation is administered to immunize patients against viral infections.

Dwg.0/18

TECH UPTX: 20020722

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred **Vaccines**: The **split** enveloped virus preparation comprises viral membrane fragments, viral membrane envelope proteins, viral matrix and nucleoproteins. The **vaccine** preparation additionally comprises another **split** viruses selected from **influenza** virus, respiratory syncytial virus, parainfluenza virus, metapneumovirus, measles virus, mumps virus, Epstein Barr virus, herpes virus, cytomegalovirus, dengue virus, yellow fever virus, tick-borne encephalitis virus, Japanese encephalitis virus, rubella virus, eastern, western and Venezuelan equine encephalitis viruses, and human immunodeficiency virus (HIV). The **vaccine** additionally comprises one or more residual splitting agents selected from laureth 9, NaDOC (preferred), Sarkosyl group (preferred), **Tween** 80TM and **Triton** X100TM. The **vaccine** additionally comprises a stabilizing agent, especially a **surfactant** (either singly or a mixture of polyoxyethylene sorbitan monooleate (**Tween** 80TM), t-**octylphenoxypolyethoxyethanol** (**Triton** X100TM) and polyoxyethylene-9-lauryl 5 ether. The **vaccine** is formulated to be delivered intranasally, intramuscularly or subcutaneously, transdermally, intradermally (preferred), intra-epithelially or transcutaneously. The **vaccine** may further comprise an adjuvant, such as polyoxyethylene-9-lauryl ether. Preferably, the adjuvant is a preferential stimulator of TH1 cell response, preferably 3D-MPL, QS21, a mixture of QS21 and cholesterol, and/or a CpG oligonucleotide. The adjuvant may be a vesicular adjuvant formulation comprising cholesterol, a saponin and an LPS derivative. (I) Is immunogenic in both seropositive and seronegative patients. Preferred Methods: The **split** virus preparation is admixed with a stabilising agent comprising at least one **surfactant** selected from polyoxyethylene sorbitan monooleate (**Tween** 80TM); t-**octylphenoxypolyethoxyethanol** (**Triton** X100TM) and/or polyoxyethylene-9-lauryl.ether. In method (V) the **vaccine** is administered by intradermal or intranasal route.

L21 ANSWER 4 OF 12 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2003-167101 [16] WPIDS
DNC C2003-043282
TI Device useful for intradermal delivery of a flu vaccine comprises container, needle and limiter.
DC A96 B04 B07 D16
IN ALCHAS, P; GARCON, N; SLAOUI, M M; VAN HOECKE, C
PA (BECT) BECTON DICKINSON & CO; (GLAX) GLAXOSMITHKLINE BIOLOGICALS SA
CYC 100
PI WO 2002087494 A2 20021107 (200316)* EN 42p

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW

DE 10293048 T 20030731 (200357)
GB 2386072 A 20030910 (200360)

ADT WO 2002087494 A2 WO 2002-US10938 20020405; DE 10293048 T DE 2002-10293048 20020405, WO 2002-US10938 20020405; GB 2386072 A WO 2002-US10938 20020405, GB 2003-6611 20030321

FDT DE 10293048 T Based on WO 2002087494; GB 2386072 A Based on WO 2002087494

PRAI US 2001-286821P 20010427

AN 2003-167101 [16] WPIDS

AB WO 200287494 A UPAB: 20030307

NOVELTY - Intradermal delivery device (A) which comprises:

(a) Container comprising a flu vaccine and having outlet port (p);

(b) Needle in fluid communication with (p); and

(c) Limiter surrounding (B).

is new.

DETAILED DESCRIPTION - Intradermal delivery device (A) which comprises:

(a) Container comprising a flu vaccine and having outlet port (p);

(b) Needle in fluid communication with (p), having forward end (fe) adapted to penetrate skin; and

(c) Limiter surrounding (B), having skin engaging surface (s) adapted to be received against the skin to receive an intradermal injection. (fe) extends beyond (s) a selected distance such that (C) limits an amount which (B) is able to penetrate through the skin.

is new.

INDEPENDENT CLAIMS are included for the following:

(1) A kit for use in intradermal flu vaccine (v) delivery comprising a vaccine container comprising (v) and a hypodermic needle assembly comprising a hub portion which is able to attached to a drug container, (B) and (C);

(2) Preparation of (v) involving:

(i) harvesting of virus-containing material from a culture;

(ii) clarifying the harvested material to remove non-virus material;

(iii) concentrating the harvested virus;

(iv) separating whole virus from non-virus material; and

(v) splitting the whole virus using a splitting agent in a density gradient centrifugation step and

(vi) filtering to remove undesired material (the steps are performed in order but not necessarily consecutively).

ACTIVITY - Virucide.

MECHANISM OF ACTION - Vaccine; Haemagglutination inhibitor.

USE - For intradermal delivery of a flu **vaccine** to animal e.g. human (claimed). The **vaccine** is **influenza vaccine.**

ADVANTAGE - The **influenza** virus **vaccine** preparation stimulates systemic immunity at a protective level with a low dose of antigen (1 - 5 mu g). The international criteria for an effective flu **vaccine** are met. Thus intradermal administration of low antigen dose **vaccine** can produce a systemic seroconversion (4-fold increase in anti-HA titres) equivalent to that obtained by s.c. administration of the same **vaccine.**

Dwg.0/7

TECH UPTX: 20030307

TECHNOLOGY FOCUS - INSTRUMENTATION AND TESTING - Preferred Device: The

device includes a hub portion (H1) and a sealing membrane (M1). (C) and (H1) are integrally formed into a single piece structure made from a plastic material or as separate pieces. The selected distance is fixed (0.5 - 3 mm) and much less than the length of (B). (A) is pre-filled with a substance.
Preferred Components: (A) is a syringe including a generally hollow, cylindrical body portion and a plunger (l) that is received with a reservoir (r). (l) is selectively movable within (r) to cause the substance to be forced out of the outlet portion during an injection. (r) contains vaccine. The syringe has a flat body portion that at least partially surrounding (r). The body portion and (r) are made from two sheets of thermoplastic material such that side walls of (r) are selectively detected toward each other to expel a substance from (r) during an injection. A receiver adjacent to (p) is circular. (H1) supports (B) and is selectively secured to (A) near (p). (H1) is completely received within the receiver. (C) is integrally formed with the receiver such that (C) is permanently supported to the body portion adjacent to (p) or (C) is formed separately from the receiver and is partially received by the receiver. (C) includes an inner cavity that receives at least a portion of (H1) and the cavity includes an abutment surface that engages corresponding structure on (H1) thus limiting the amount that (fe) extends beyond (s). (C) is integrally formed as part of the syringe and (H1) is received within the limiter portion. (s) surrounds (B) and has a inner diameter at least five times greater than an outside diameter of (B). (s) is circular, flat or continuous and extends through a plane that is perpendicular to an axis of (B). (s) includes a central opening, which is larger than an outside dimension of (B) and also includes a contact surface area which is large enough to stabilize the assembly in a desired orientation relative to the skin. The desired orientation is perpendicular to the skin. (fe) extends away from (H1) in a first direction and a needle back end (be) extends away from (H1) in a second direction. (M1) closes (p) and (be) pierces (M1), when (H1) is received by the receiver.
Preferred Vaccine: (v) is a trivalent non-live vaccine. The virus is grown on embryonated hen eggs and the harvested material is allantoic fluid. (v) meets the EU criteria for at least two strains. (v) additionally comprises a bile acid or cholic acid or their derivative such as sodium deoxycholate. (v) comprises at least one non-ionic **surfactant.**

TECHNOLOGY FOCUS - INORGANIC CHEMISTRY - Preferred Method: The clarification is performed by centrifugation at a moderate speed. The concentration employs an adsorption method such as CaHPO4 adsorption. The separation step is a zonal centrifugation separation using a sucrose gradient. The splitting is performed in a further sucrose gradient containing splitting agent (preferably sodium deoxycholate). The filtration is an ultrafiltration, which concentrates the **split** virus material. There is at least one sterile filtration step, optionally at the end of the process. An inactivation step is performed prior to the final filtration step. The method additionally involves adjusting the concentration of at least one detergent in the vaccine composition.

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred **Surfactant**: At least one non-ionic **surfactant** is **Triton** (octyl- or nonylphenoxy polyoxyethanols), **Tween** (polyoxyethylene sorbitan esters) and/or polyoxyethylene ethers or esters of formula HO(CH2CH2O)n-A-R (I) (preferably **Tween** 80 (polyoxyethylene sorbitan monooleate) and **Triton** X-100 (tert-octylphenoxy polyethoxyethanol)).
n = 1 - 50;
A = bond or -C(O)-;
R = 1-50C alkyl or phenyl (1-50C) alkyl.

L21 ANSWER 5 OF 12 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2002-706958 [76] WPIDS
DNC C2002-200536
TI Trivalent, **split influenza** antigen preparation useful for the manufacture of an intradermal flu **vaccine** for prophylactic and/or therapeutic purposes in humans.
DC B04 D16
IN GARCON, N; SLAOUI, M M; VAN HOECKE, C
PA (GLAX) GLAXOSMITHKLINE BIOLOGICALS SA; (SMIK) SMITHKLINE BEECHAM BIOLOGICALS
CYC 101
PI WO 2002067983 A1 20020906 (200276)* EN 53p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW
EP 1361889 A1 20031119 (200377) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
ADT WO 2002067983 A1 WO 2002-EP1843 20020221; EP 1361889 A1 EP 2002-722113 20020221, WO 2002-EP1843 20020221
FDT EP 1361889 A1 Based on WO 2002067983
PRAI GB 2001-8366 20010403; GB 2001-4542 20010223
AN 2002-706958 [76] WPIDS
AB WO 200267983 A UPAB: 20021125
NOVELTY - Use of an **influenza** antigen preparation in the manufacture of an intradermal flu **vaccine.**

DETAILED DESCRIPTION - Use (M1) of an **influenza** antigen preparation, obtainable by the following process, in the manufacture of an intradermal flu **vaccine**, comprises:

(i) harvesting of virus-containing material from a culture;

(ii) clarification of the harvested material to remove non-virus material;

(iii) concentration of the harvested virus;

(iv) a further step to separate whole virus from non-virus material;

(v) splitting of the whole virus using a suitable splitting agent in a density gradient centrifugation step; and

(vi) filtration to remove undesired materials.

The steps are performed in that order but not necessarily consecutively.

An INDEPENDENT CLAIM is also included for a pharmaceutical kit comprising an intradermal delivery device and an **influenza vaccine** obtainable by the method cited above.

ACTIVITY - Virucide; Immunostimulant.

Test details are described but not results given.

MECHANISM OF ACTION - Vaccine; Gene therapy.

No supporting data provided.

USE - The trivalent, **split influenza** antigen preparation is useful for the manufacture of a **vaccine** for intradermal delivery. The intradermal **vaccine** comprises at least one non-ionic **surfactant** . The methods and compositions are also used for the manufacture in particular of an intradermal flu **vaccine** (all claimed).

Dwg.0/1
TECH UPTX: 20021125
TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Method: The intradermal flu

vaccine is a trivalent **vaccine.** The virus is grown on embryonated hen eggs and the harvested material is allantoic fluid. The clarification step is performed by centrifugation at a moderate speed. The concentration step employs an adsorption method such as CaHPO4 adsorption. The further separation step is a zonal centrifugation separation using sucrose gradient. The splitting step is performed in a further sucrose gradient, where it contains the splitting agent which is preferably sodium deoxycholate. The filtration step is an ultrafiltration step which concentrates the spilt virus material. There is at least one sterile filtration step, optionally at the end of the process. An inactivation step is performed prior to the final filtration step. The method further comprises adjusting the concentration of one or more detergents in the **vaccine** composition. The **vaccine** is provided with a dose volume between 0.1 and 0.2 ml and an antigen dose of 1-7.5 mug hemagglutinin per strain of **influenza** present. The **vaccine** further comprises an adjuvant comprising a combination of cholesterol, a saponin and an lipopolysaccharide (LPS) derivative. Preferred Kit: The intradermal delivery device of the pharmaceutical kit is a short needle delivery device.

L21 ANSWER 6 OF 12 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2002-454496 [48] WPIDS
DNC C2002-129191
TI Use of a **split** level enveloped virus preparation for manufacture of a vaccine formulation for intranasal delivery and treatment or prophylaxis of disease caused by an enveloped virus.
DC A96 B04 D16
IN COLAU, B D A; DESCHAMPS, M
PA (SMIK) SMITHKLINE BEECHAM BIOLOGICALS; (GLAX) GLAXOSMITHKLINE BIOLOGICALS SA
CYC 97
PI WO 2002028422 A2 20020411 (200248)* EN 49p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2002013984 A 20020415 (200254)
EP 1324769 A2 20030709 (200345) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
NO 2003001483 A 20030528 (200348)
KR 2003031200 A 20030418 (200353)
BR 2001014393 A 20030826 (200368)
CZ 2003000931 A3 20031015 (200374)
HU 2003002643 A2 20031128 (200405)
ADT WO 2002028422 A2 WO 2001-EP11326 20011001; AU 2002013984 A AU 2002-13984 20011001; EP 1324769 A2 EP 2001-982385 20011001, WO 2001-EP11326 20011001; NO 2003001483 A WO 2001-EP11326 20011001, NO 2003-1483 20030401; KR 2003031200 A KR 2003-704719 20030402; BR 2001014393 A BR 2001-14393 20011001, WO 2001-EP11326 20011001; CZ 2003000931 A3 WO 2001-EP11326 20011001, CZ 2003-931 20011001; HU 2003002643 A2 WO 2001-EP11326 20011001, HU 2003-2643 20011001
FDT AU 2002013984 A Based on WO 2002028422; EP 1324769 A2 Based on WO 2002028422; BR 2001014393 A Based on WO 2002028422; CZ 2003000931 A3 Based on WO 2002028422; HU 2003002643 A2 Based on WO 2002028422
PRAI GB 2000-24089 20001002
AN 2002-454496 [48] WPIDS
AB WO 200228422 A UPAB: 20020730

NOVELTY - Use of a **split** level enveloped virus preparation which is not a **split influenza** virus preparation in the manufacture of a **vaccine** formulation for intranasal delivery, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) producing a vaccine formulation (M1) comprising:

(a) splitting an enveloped virus;

(b) optionally admixing the **split** enveloped virus preparation with a stabilizing agent; and

(c) optionally admixing the **split** enveloped virus preparation with an adjuvant (carrier and/or immunostimulant);

(2) a kit for delivery of an intranasal vaccine formulation comprises a **split** enveloped virus preparation and an intranasal delivery device; and

(3) an intranasal delivery device comprising a vaccine; and

(4) a method, use or kit comprising a vaccine formulation that is immunogenic in seropositive and seronegative individuals.

ACTIVITY - Virucide.

No supporting data available.

MECHANISM OF ACTION - Vaccine (claimed).

8 week old female BALB/c mice were used to test the immunogenicity of the **split** RSV (Respiratory Syncytial Virus) preparation administered intranasally in a volume 60 micro l (2 x 30 micro l). Results showed that a potent anti-FG antibody response was induced by 2 vaccinations with **split** RSV antigen administered intranasally.

USE - For the treatment or prophylaxis of disease, especially to protect a mammal susceptible to, or suffering from a disease caused by an enveloped virus (claimed).

ADVANTAGE - Provides a suitable vaccine that is safe and effective for intranasal delivery reducing the need for painful injections and associated negative effect of patient compliance.

Dwg.0/16

TECH UPTX: 20020730

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Vaccine: The **split** enveloped virus preparation is an individual or a mixture of respiratory syncytial virus, parainfluenza virus, measles and herpes simplex virus. The **split** enveloped virus preparation comprises viral membrane fragments, viral membrane envelope proteins, viral matrix and nucleoproteins and may also comprise one or more residual splitting agents,a stabilising agent and an adjuvant.

Preferred Device: The device is a pressure threshold device.

TECHNOLOGY FOCUS - POLYMERS - Preferred Agents: The splitting agents may be selected from laureth 9, Na DOC, Sarcosyl group, **Tween** 80 (RTM) and **Triton** X100 (RTM), preferably, NaDOC or Sarcosyl.

The stabilizing agent is preferably a **surfactant** which is either singly or a mixture of polyoxyethylene sorbitan monooleate (**TWEEN** 80) (RTM), **TRITON** X100 (RTM; t-**octylphenoxypolyethoxyethano** l) and polyoxyethylene-9-lauryl ether.

L21 ANSWER 7 OF 12 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN DUPLICATE 4

AN 2001-299981 [31] WPIDS

CR 2001-308048 [32]; 2001-397498 [42]

DNC C2001-092055

TI Non-live **influenza** virus antigen composition is used in the preparation of a one-dose intranasal **vaccine.**

DC A25 A96 B04 D16

IN FRIEDE, M; HENDERICKX, V; HERMAND, P; SLAOUI, M M; THOELEN, S G J; THOELEN, J G S

PA (SMIK) SMITHKLINE BEECHAM BIOLOGICALS

CYC 95
PI WO 2001021151 A1 20010329 (200131)* EN 63p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2000077825 A 20010424 (200141)
BR 2000014281 A 20020521 (200238)
EP 1214054 A1 20020619 (200240) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
NO 2002001431 A 20020424 (200241)
CZ 2002001044 A3 20020814 (200263)
KR 2002038771 A 20020523 (200274)
HU 2002002846 A2 20021228 (200308)
JP 2003509451 W 20030311 (200319) 66p
CN 1391463 A 20030115 (200330)
AU 764368 B 20030814 (200363)
MX 2002003069 A1 20021001 (200370)
NZ 517903 A 20031031 (200380)
ZA 2002002269 A 20031231 (200408)# 71p
ADT WO 2001021151 A1 WO 2000-EP9367 20000922; AU 2000077825 A AU 2000-77825 20000922; BR 2000014281 A BR 2000-14281 20000922, WO 2000-EP9367 20000922; EP 1214054 A1 EP 2000-967781 20000922, WO 2000-EP9367 20000922; NO 2002001431 A WO 2000-EP9367 20000922, NO 2002-1431 20020321; CZ 2002001044 A3 WO 2000-EP9367 20000922, CZ 2002-1044 20000922; KR 2002038771 A KR 2002-703833 20020323; HU 2002002846 A2 WO 2000-EP9367 20000922, HU 2002-2846 20000922; JP 2003509451 W WO 2000-EP9367 20000922, JP 2001-524577 20000922; CN 1391463 A CN 2000-815945 20000922; AU 764368 B AU 2000-77825 20000922; MX 2002003069 A1 WO 2000-EP9367 20000922, MX 2002-3069 20020322; NZ 517903 A NZ 2000-517903 20000922, WO 2000-EP9367 20000922; ZA 2002002269 A ZA 2002-2269 20020320
FDT AU 2000077825 A Based on WO 2001021151; BR 2000014281 A Based on WO 2001021151; EP 1214054 A1 Based on WO 2001021151; CZ 2002001044 A3 Based on WO 2001021151; HU 2002002846 A2 Based on WO 2001021151; JP 2003509451 W Based on WO 2001021151; AU 764368 B Previous Publ. AU 2000077825, Based on WO 2001021151; MX 2002003069 A1 Based on WO 2001021151; NZ 517903 A Based on WO 2001021151
PRAI GB 2000-16686 20000706; GB 1999-22700 19990924; GB 1999-22703 19990924; ZA 2002-2269 20020320
AN 2001-299981 [31] WPIDS
CR 2001-308048 [32]; 2001-397498 [42]
AB WO 200121151 A UPAB: 20040202
NOVELTY - A novel non-live **influenza** virus antigen composition is used in the manufacture of a one-dose intranasal **vaccine** (I) which generates an immune response that meets international regulatory requirements for **influenza vaccines.**

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) preventing influenza infection or disease in a subject comprising administering (I) via the mucosal surface to induce an immune response, which meets at least 2 of the following criteria:

(a) a seroconversion rate of at least 40%;

(b) a seroprotection rate at least 70%; and

(c) a conversion factor of at least 2.5;

(2) preventing influenza infection or disease in a subject comprising administering a low haemagglutinin (HA)-(I) (I') via the mucosal surface to induce an immune response, which meets at least 2 of the following criteria:

(1) a seroconversion rate of at least 40%;
(2) a seroprotection rate at least 70%; and
(3) a conversion factor of at least 2.5;
(3) a pharmaceutical kit comprising an intranasal delivery device comprising (I) without an added immunostimulant;
(4) a pharmaceutical kit comprising an intranasal delivery device comprising (I'); and
(5) a method for preparing (I), comprising:
(a) providing a **split** influenza virus composition produced by conventional means, comprising at least 1 non-ionic **surfactant**;
(b) adjusting the concentration of HA and of non-ionic **surfactant**; and
(c) filling an intranasal device with resulting vaccine, especially in a bi-dose format.
ACTIVITY - Virucide.
MECHANISM OF ACTION - Vaccine.
USE - (I) is used in preventing influenza infection or disease.
ADVANTAGE - The influenza antigen can be provided at a significantly lower dose than indicted in the prior art.
Dwg.0/4

TECH UPTX: 20010607
TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred **vaccine**: (I) meets at least two of the three European Union criteria for seroconversion rate for all the **influenza** strains within the **vaccine.** The **influenza** virus antigen composition is selected from **split** virus antigen preparations, subunit antigens, chemically or otherwise inactivated whole virus. The **surfactant** is selected from **octylphenoxypolyethoxyethanols**, polyoxyethylene sorbitan esters and/or polyoxyethylene ethers. (I) further comprises a bile acid or cholic acid or their derivatives. (I) has a low HA content of at most 30 (especially 7.5) microg. (I) further comprises a non-toxic derivative lipid A, especially derivatives of monophosphoryl lipid (MPL) A, especially 3D-MPL and laureth 9.

L21 ANSWER 8 OF 12 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2001-308048 [32] WPIDS
CR 2001-299981 [31]; 2001-397498 [42]
DNC C2001-095129
TI Adjuvant system comprising a polyoxyethylene sorbitan ester **surfactant** in combination with an octoxynol, useful for preparing a vaccine for treating a mammal suffering from or susceptible to a pathogenic infection, cancer, or allergy.
DC A96 B04 D16
IN FRIEDE, M; HENERICKX, V; HERMAND, P; HENDERICKX, V
PA (SMIK) SMITHKLINE BEECHAM BIOLOGICALS; (SMIK) SMITHKLINE BEECHAM BIOLOGICS SA
CYC 95
PI WO 2001021207 A2 20010329 (200132)* EN 26p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2000079070 A 20010424 (200141)
BR 2000014282 A 20020521 (200238)
NO 2002001433 A 20020521 (200240)
EP 1221971 A2 20020717 (200254) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT

RO SE SI
CZ 2002001043 A3 20020814 (200263)
KR 2002038770 A 20020523 (200274)
HU 2002002885 A2 20021228 (200308)
JP 2003509473 W 20030311 (200319) 33p
CN 1391483 A 20030115 (200330)
ZA 2002002270 A 20030430 (200334)# 36p
MX 2002003067 A1 20021001 (200370)
AU 765824 B 20031002 (200373)

ADT WO 2001021207 A2 WO 2000-EP9366 20000922; AU 2000079070 A AU 2000-79070 20000922; BR 2000014282 A BR 2000-14282 20000922, WO 2000-EP9366 20000922; NO 2002001433 A WO 2000-EP9366 20000922, NO 2002-1433 20020321; EP 1221971 A2 EP 2000-969296 20000922, WO 2000-EP9366 20000922; CZ 2002001043 A3 WO 2000-EP9366 20000922, CZ 2002-1043 20000922; KR 2002038770 A KR 2002-703832 20020323; HU 2002002885 A2 WO 2000-EP9366 20000922, HU 2002-2885 20000922; JP 2003509473 W WO 2000-EP9366 20000922, JP 2001-524631 20000922; CN 1391483 A CN 2000-816014 20000922; ZA 2002002270 A ZA 2002-2270 20020320; MX 2002003067 A1 WO 2000-EP9366 20000922, MX 2002-3067 20020322; AU 765824 B AU 2000-79070 20000922

FDT AU 2000079070 A Based on WO 2001021207; BR 2000014282 A Based on WO 2001021207; EP 1221971 A2 Based on WO 2001021207; CZ 2002001043 A3 Based on WO 2001021207; HU 2002002885 A2 Based on WO 2001021207; JP 2003509473 W Based on WO 2001021207; MX 2002003067 A1 Based on WO 2001021207; AU 765824 B Previous Publ. AU 2000079070, Based on WO 2001021207

PRAI GB 2000-16685 20000706; GB 1999-22703 19990924; ZA 2002-2270 20020320

AN 2001-308048 [32] WPIDS

CR 2001-299981 [31]; 2001-397498 [42]

AB WO 200121207 A UPAB: 20031112

NOVELTY - An adjuvant system (I) comprising a polyoxyethylene sorbitan ester **surfactant** in combination with an octoxynol for application to a mucosal surface of a patient, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a method (M1) of producing a vaccine, comprising admixing a polyoxyethylene sorbitan ester, an octoxynol and an antigen, and providing the vaccine in the form of a vaccine dose for mucosal administration;

(2) a spray or aerosol device, more particularly a bi-dose device, filled with a vaccine comprising a polyoxyethylene sorbitan ester, an octoxynol and an antigen; and

(3) a method (M2) of treating a mammal suffering from or susceptible to a pathogenic infection, or cancer, or allergy, comprising administering to the mucosa of the mammal a safe and effective amount of a vaccine composition comprising a polyoxyethylene sorbitan ester, an octoxynol and an antigen.

ACTIVITY - Cytostatic; antiallergic; antimicrobial.

MECHANISM OF ACTION - Vaccine.

Priming was done in female Balb/c mice (8 weeks old) at day 0 by administering with a pipette (under anesthesia) in each nostril 2.5 micrograms haemagglutin (HA) of beta-propiolactone (BPL)-inactivated-A/Beijing/262/95 **influenza** virus contained in 10 microlitres phosphate buffered saline (PBS). After 28 days, mice (6 animals/group) were boosted intranasally (under anesthesia) with 20 microlitres of solution (10 microlitres per nostril, delivered as droplets by pipette) containing 5 micrograms HA of BPL-inactivated-A/Beijing/262/95 **influenza** virus in either PBS, TWEEN80 (0.11%) plus **Triton** X-100 (0.074%), or by intramuscular injection of 1.5 micrograms **influenza vaccine.** Antigens were supplied by SSD GmBH manufacturer, Germany). Haemagglutination inhibition (HAI) antibody (Ab) responses were measured in sera. When formulated with TWEEN80 and

Triton, sum **influenza** virus delivered intranasally was capable of boosting pre-HAI Ab responses as efficiently as the classical parenteral **influenza vaccine.** However, the same antigen given intranasally in the absence of TWEEN80 and **Triton** was significantly less immunogenic.

USE - (I) together with an antigen is useful in the manufacture of a **vaccine** for mucosal administration. (I) is used for the manufacture of a **vaccine** for use in medicine, preferably for prophylaxis against **influenza.**

A vaccine comprising (I) is useful for treating a mammal suffering from or susceptible to a pathogenic infection, or cancer, or allergy (all claimed).

ADVANTAGE - (I) is safe and easy to use.

Dwg.0/1

TECH UPTX: 20010611

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Adjuvant System: The polyoxyethylene sorbitan ester is polyoxyethylene sorbitan monooleate (TWEEN80) (RTM). The octoxynol is t-**octylphenoxypolyethoxyethanol** (**TRITON** X-100) (RTM). (I) further comprises a bile salt or a cholic acid derivative. (I) together with an antigen is useful in the manufacture of a **vaccine** for mucosal administration.

The antigen is Human Immunodeficiency Virus, Varicella Zoster virus, Herpes Simplex Virus type 1, Herpes Simplex virus type 2, Human cytomegalovirus, Dengue virus, Hepatitis A, B, C or E, Respiratory Syncytial virus, human papilloma virus, **Influenza** virus, Hib, Meningitis virus, Salmonella, Neisseria, Borrelia, Chlamydia, Bordetella, Streptococcus, Mycoplasma, Mycobacteria, Haemophilus, Plasmodium or Toxoplasma, stanworth decapeptide or Tumor associated antigens (TMA), MACE, BAGE, GAGE, MUC-1, Her-2 neu, LnRH, CEA (carcinoembryonic antigen), PSA (prostate specific antigen), KSA, or PRAME. Preferably, the antigen is an antigen or antigenic preparation from a **split influenza** virus preparation.

Preferred Method: In M1, the **vaccine** is provided in an intranasal aerosol or spray device. In M2, the **vaccine** is an **influenza** virus **vaccine** comprising an **influenza** antigen or antigenic preparation, such as a **split influenza** virus preparation.

Preferred Device: The antigen is an **influenza** antigen or antigenic preparation from a **split influenza** virus preparation.

L21 ANSWER 9 OF 12 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2001-397498 [42] WPIDS
CR 2001-299981 [31]; 2001-308048 [32]
DNC C2001-120803
TI Adjuvant composition useful for treating viral, bacterial, parasitic infections, allergy, or cancer, comprises polyoxyethylene alkyl ether or ester, and additional non-ionic **surfactant.**
DC A25 A96 B04 D16
IN FRIEDE, M; HENDERICKX, V; HERMAND, P
PA (SMIK) SMITHKLINE BEECHAM BIOLOGICALS
CYC 95
PI WO 2001021152 A1 20010329 (200142)* EN 35p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2000075226 A 20010424 (200142)

BR 2000014285 A 20020521 (200238)
EP 1214053 A1 20020619 (200240) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
NO 2002001432 A 20020521 (200240)
CZ 2002001045 A3 20020814 (200263)
KR 2002048942 A 20020624 (200281)
JP 2003509452 W 20030311 (200319) 44p
HU 2002003817 A2 20030328 (200333)
ZA 2002002268 A 20030430 (200334)# 46p
CN 1399539 A 20030226 (200337)
NZ 517901 A 20030829 (200365)
MX 2002003068 A1 20021001 (200370)
AU 766635 B 20031023 (200381)

ADT WO 2001021152 A1 WO 2000-EP9368 20000922; AU 2000075226 A AU 2000-75226 20000922; BR 2000014285 A BR 2000-14285 20000922, WO 2000-EP9368 20000922; EP 1214053 A1 EP 2000-964232 20000922, WO 2000-EP9368 20000922; NO 2002001432 A WO 2000-EP9368 20000922, NO 2002-1432 20020321; CZ 2002001045 A3 WO 2000-EP9368 20000922, CZ 2002-1045 20000922; KR 2002048942 A KR 2002-703856 20020325; JP 2003509452 W WO 2000-EP9368 20000922, JP 2001-524578 20000922; HU 2002003817 A2 WO 2000-EP9368 20000922, HU 2002-3817 20000922; ZA 2002002268 A ZA 2002-2268 20020320; CN 1399539 A CN 2000-816263 20000922; NZ 517901 A NZ 2000-517901 20000922, WO 2000-EP9368 20000922; MX 2002003068 A1 WO 2000-EP9368 20000922, MX 2002-3068 20020322; AU 766635 B AU 2000-75226 20000922

FDT AU 2000075226 A Based on WO 2001021152; BR 2000014285 A Based on WO 2001021152; EP 1214053 A1 Based on WO 2001021152; CZ 2002001045 A3 Based on WO 2001021152; JP 2003509452 W Based on WO 2001021152; HU 2002003817 A2 Based on WO 2001021152; NZ 517901 A Based on WO 2001021152; MX 2002003068 A1 Based on WO 2001021152; AU 766635 B Previous Publ. AU 2000075226, Based on WO 2001021152

PRAI GB 2000-16647 20000706; GB 1999-22700 19990924; ZA 2002-2268 20020320

AN 2001-397498 [42] WPIDS

CR 2001-299981 [31]; 2001-308048 [32]

AB WO 200121152 A UPAB: 20031216

NOVELTY - An adjuvant composition (I) comprising polyoxyethylene alkyl ether or ester (P), and an additional non-ionic **surfactant.**

DETAILED DESCRIPTION - (P) is of formula (F'):

HO(CH2CH2O)n-A-R (F')

n = 1-50;

A = a bond or -C(O)-; and

R = 1-50C alkyl or phenyl 1-50C alkyl.

INDEPENDENT CLAIMS are also included for the following:

(1) an adjuvant combination (II) comprising (I) in combination with at least one additional immunostimulant;

(2) a vaccine (III) comprising (I) or (II), and further comprising an antigen;

(3) a spray device (IV), more particularly a bi-dose spray device, filled with (III); and

(4) preparation of (III).

ACTIVITY - Antibacterial; virucide; antiallergic; cytostatic; immunosuppressive.

MECHANISM OF ACTION - Vaccine (claimed).

An open, controlled and randomized study evaluated the immunogenicity of an intranasal **split influenza vaccine** formulated with laureth 9 supplemented with TWEEN80 and **triton** -X-100 compared to the conventional parenteral **vaccine.** Twenty healthy adult subjects received one dose of Fluarix and ten subjects received one dose of the intranasal **influenza vaccine.**

The immunogenicity of the **vaccines** was examined by assessing the serum hemagglutination inhibition (HI) titers to determine seroconversion rate, conversion factor and seroprotection rate. The immunogenicity results showed that the intranasal formulation produced similar levels of seropositivity, seroconversion and seroprotection to the conventional parenteral **vaccine** Fluarix twenty-one days after one dose. The intranasal formulation generally produced a better mucosal IgA response after one dose than the conventional parenteral **vaccine.**

USE - (I) or (II) is useful in the manufacture of a medicament for application onto a mucosal surface or the skin of a patient. (III) is useful for treating a mammal suffering from or susceptible to viral, bacterial, parasitic infections, allergy, or cancer (claimed). (I), (II) and (III) are useful for treating autoimmune diseases.

ADVANTAGE - (I) is safe, potent and is easily manufactured.

Dwg.0/0

TECH UPTX: 20010726

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preparation: (III) is prepared by admixing (I) or (II), an excipient, and an antigen or antigenic composition (claimed).

Preferred Composition: In (I), the additional non-ionic **surfactant** is an Octoxynol, preferably t-**octylphenoxypolyethoxyethanol** (**TRITON** X100). (I) additionally comprises one or both of a polyoxyethylene sorbitan ester, cholic acid or its derivative. (P) is hemolytic, and the degree of hemolytic activity is in the range of 0.05-0.0001 % as measured in the Guinea Pig blood hemolysis assay. (P) has a hemolytic activity within a ten fold difference to that of polyoxyethylene-9 lauryl ether or polyoxyethylene-8 stearyl ether. (P) is selected from polyoxyethylene-9-lauryl ether, polyoxyethylene-9-lauryl ester polyoxyethylene-9-stearyl ether, polyoxyethylene-8-stearyl ether polyoxyethylene-4-lauryl ether, polyoxyethylene-35-lauryl ether, and polyoxyethylene-23-lauryl ether. The total concentration of detergent present is in the range 0.001-10 %, preferably 0.001-0.7 %. In (II), the additional immunostimulant is selected from LT, CT, 3D-MPL, QS21 and CpG, where CpG is TCCATGACGTTCCTGACGTT.

Preferred **Vaccine**: In (III), the antigen is selected from human immunodeficiency virus, varicella zoster virus, herpes simplex virus type 1, herpes simplex virus type 2, human cytomegalovirus, dengue virus, hepatitis A, B, C or E, respiratory syncytial virus, human papilloma virus, **influenza** virus, hib, meningitis virus, Salmonella, Neisseria, Borrelia, Chlamydia, Bordetella, Streptococcus, Mycoplasma, Mycobacteria, Haemophilus, Plasmodium or Toxoplasma, stanworth decapeptide, or tumor associated antigens (TMA), MAGE, BAGE, GAGE, MUC-1, Her-2 neu, LnRH, CEA, PSA, KSA, or PRAME. (III) is in the form of an aerosol or spray.

L21 ANSWER 10 OF 12 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2000:467740 CAPLUS
DN 133:355041
TI A **Triton** X-100-**split** virion influenza vaccine is safe and fulfills the committee for proprietary medicinal products (CPMP) recommendations for the European Community for immunogenicity, in children, adults and the elderly
AU Lina, Bruno; Fletcher, Mark A.; Valette, Martine; Saliou, Pierre; Aymard, Michele
CS Laboratoire de Virologie, Faculte de Medecine Lyon Grange Blanche, Lyon, F-69373, Fr.
SO Biologicals (2000), 28(2), 95-103
CODEN: BILSEC; ISSN: 1045-1056
PB Academic Press
DT Journal

LA English
AB Influenza epidemics are an important cause of morbidity and mortality throughout the world. Current recommendations from Health Authorities emphasize annual immunization of people who are particularly at risk from an influenza virus infection; however, vaccination of working adults and of school children also has been shown to provide public health benefits. To give it a more advantageous reactogenicity profile than the di-Et ether-**split** influenza vaccines available previously, a **split** virion influenza vaccine has been produced with TritonX-100. In a series of clin. trials, Aventis Pasteur (formerly, Pasteur Merieux Connaught) tested both the safety and immunogenicity of this TritonX-100-**split** virion influenza vaccine in 566 subjects (42 children, 296 adults, and 228 elderly adults) during three influenza seasons (1991, 1993, and 1995). The TritonX-100-**split** virion vaccine was well tolerated: no serious adverse events were recorded during the 21 days following immunization. Among the local reactions observed, mild pain, redness, or induration at the injection site were the most frequently reported. Fever (38.0 to 38.5°C) was noted in five adults or elderly subjects (1%), and in two children (5%). Immunogenicity was determined by measuring serum hemagglutinin antibody titers specific to each vaccine virus strain. In each of the three vaccination campaigns, the TritonX-100-**split** virion influenza vaccine fulfilled the Notes for Guidance on Harmonization of Requirements for Influenza Vaccines outlined by the Committee for Proprietary Medicinal Products (CPMP) of the European Community for an influenza virus vaccine (i.e., seroprotection, seroconversion, or increase of geometric mean titer) in all age groups. (c) 2000 The International Association of Biological Standardization.
IT Development, mammalian postnatal
(child; evaluation of **Triton** X-100-**split** virion influenza vaccine for immunogenicity in children, adults and elderly)
IT Aging, animal
(elderly; evaluation of **Triton** X-100-**split** virion influenza vaccine for immunogenicity in children, adults and elderly)
IT **Influenza virus**
Vaccines
(evaluation of **Triton** X-100-**split** virion **influenza** vaccine for immunogenicity in children, adults and elderly)
IT Hemagglutinins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(hemagglutinin; evaluation of **Triton** X-100-**split** virion influenza vaccine for immunogenicity in children, adults and elderly)
IT Antibodies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(hemagglutinins; evaluation of **Triton** X-100-**split** virion influenza vaccine for immunogenicity in children, adults and elderly)
IT **9002-93-1**, **Triton** X-100
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(evaluation of **Triton** X-100-**split** virion influenza vaccine for immunogenicity in children, adults and elderly)
RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 11 OF 12 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1984:49697 CAPLUS
DN 100:49697

TI The quantification of the hemagglutinin content of **influenza** whole **virus** and **Tween**-ether **split** vaccines
AU Johannsen, Roloff; Moser, Hans; Hinz, Juergen; Friesen, Heinz Juergen; Gruschkau, Horst
CS Res. Lab., Behringwerke A.-G., Marburg, D-3550, Fed. Rep. Ger.
SO Journal of Biological Standardization (1983), 11(4), 341-52
CODEN: JBSTBI; ISSN: 0092-1157
DT Journal
LA English
AB Monovalent whole virus and Tween-Et2O **split** vaccines prepared from influenza A/Bangkok, A/Brazil, and B/Singapore viruses were assayed for hemagglutinin content by single radial immunodiffusion (SRID), quant. SDS-polyacrylamide gel electrophoresis (SDS-PAGE), and immunization of guinea pigs. When SRID was performed with **split** vaccines, hemagglutinin values were obtained which were 25-50% of those obtained before virion disruption; when, however, disruption was conducted in excess detergent, thus preventing aggregate formation by solubilized hemagglutinin, test values comparable with those of whole-virus vaccines were obtained. In agreement with these results, immunization expts. revealed that whole-virus and corresponding **split** vaccines exhibited comparable immunogenicity in guinea pigs. Addnl., it could be calculated from SDS-PAGE and densitometer tracings, obtained by scanning the gels after staining with either Coomassie Blue or FITC-Con A, that 90-95% of whole-virus hemagglutinin was recovered in Tween-Et2O **split** vaccines. It is concluded that precise quantification of Tween-Et2O **split** vaccines is not possible by the SRID test alone. Since aggregate formation by solubilized hemagglutinin occurs, either a physicochem. method including a disaggregation procedure, such as SDS treatment, or immunol. evaluation of the original whole-virus preparation before disruption of virions should be applied as an addnl. criterion for quantification of influenza Tween-Et2O **split** vaccines.
IT **Vaccines**
(for **influenza virus**, determination of hemagglutinin content of, methods for)
IT Agglutinins and Lectins
RL: BIOL (Biological study)
(hemagglutinins, of **influenza virus** vaccine, methods for determination of)
IT **Virus**, animal
(**influenza**, vaccine to, determination of hemagglutinin in, methods for)

L21 ANSWER 12 OF 12 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 1975-29077W [18] WPIDS
TI Vaccines from pyretogenic virus fragments - after splitting the virus with hemolytic **surfactant** in an ultracentrifuge.
DC B04 D16
PA (DUNC) DUNCAN FLOCKHART CO; (DUNC) FLOCKHART & CO LTD DUNCAN
CYC 15
PI BE 821175 A 19750417 (197518)*
DE 2449530 A 19750430 (197519)
NL 7413642 A 19750422 (197519)
NO 7403758 A 19750512 (197524)
SE 7413113 A 19750520 (197524)
DK 7405439 A 19750616 (197529)
FR 2248054 A 19750620 (197530)
JP 50082228 A 19750703 (197535)
AT 7408350 A 19760515 (197624)
ZA 7406398 A 19760408 (197631)
GB 1486557 A 19770921 (197738)

IL 45870 A 19780310 (197814)
CA 1050886 A 19790320 (197913)
US 4158054 A 19790612 (197926)
CH 611518 A 19790615 (197929)
DE 2449530 C 19850808 (198533)
NL 181553 B 19870416 (198719)
PRAI GB 1973-48685 19731018
AN 1975-29077W [18] WPIDS
AB BE 821175 A UPAB: 19930831
Vaccines are prepared from pyretogenic fragments of viruses isolated by introducing a liquid containing a whole inactive virus into a continuously fed zone ultracentrifuge containing a solution of graduated density,
which solution comprises a hemolytic **surfactant**, such that the virions passing across the density gradient are **split** by the **surfactant** and the antigen fragments are collected in bands of the same density. Process is used in preparation of **influenza** and similar viral **vaccines**, e.g. orthomyxovirus and paramyxovirus **vaccines** with reduced hypersensitivity.

=>

=> d his

(FILE 'WPIDS, CAPLUS' ENTERED AT 14:50:07 ON 05 FEB 2004)
DEL HIS Y

FILE 'BIOSIS' ENTERED AT 14:51:36 ON 05 FEB 2004
L1 6457 S INFLUENZ? (S) VACCIN?

FILE 'REGISTRY' ENTERED AT 14:51:56 ON 05 FEB 2004
L2 3 S 9002-93-1 OR 9002-92-0 OR 9005-65-6

FILE 'BIOSIS' ENTERED AT 14:52:44 ON 05 FEB 2004
L3 4779 S L2
L4 22438 S TRITON OR TWEEN
L5 4780 S L1/TI,ST
L6 25 S L5 AND (L3 OR L4)
L7 23074 S SPLIT
L8 165 S L5 AND L7
L9 17 S L8 AND (L3 OR L4)
L10 17 S L6 AND SPLIT
L11 1 S L8 AND SURFACTANT?
L12 18 S L9 OR L10 OR L11

FILE 'MEDLINE' ENTERED AT 14:55:31 ON 05 FEB 2004
L13 3986 S L2
E INFLUENZA VIRUS/CT
E E2+ALL
E INFLUENZA VACCINE/CT
E E3+ALL
L14 6104 S INFLUENZA VACCINE/CT
E VIRAL VACCINES+NT/CT
E INFLUENZA VIRUS/CT
E E3+ALL
L15 17257 S ORTHOMYXOVIRIDAE+NT/CT
E VACCINES/CT
E E3+NT/CT
L16 5613 S VACCINES, ATTENUATED+NT/CT

```
L17       13534 S VIRAL VACCINES/CT
L18         748 S L15 AND (L16 OR L17)
L19        4547 S L14/MAJ
                E SURFACTANTS/CT
                E E3+ALL
                E E2+ALL
L20       60023 S SURFACE"-"ACTIVE AGENTS+NT/CT
L21           8 S L18 AND L20
L22          47 S L19 AND L20
L23           3 S L19 AND L13
L24          11 S L22 AND SPLIT
L25          19 S L24 OR L23 OR L21

     FILE 'MEDLINE, BIOSIS' ENTERED AT 15:16:00 ON 05 FEB 2004
L26          32 DUP REM L25 L12 (5 DUPLICATES REMOVED)

=> fil medline biosis
FILE 'MEDLINE' ENTERED AT 15:16:16 ON 05 FEB 2004

FILE 'BIOSIS' ENTERED AT 15:16:16 ON 05 FEB 2004
COPYRIGHT (C) 2004 BIOLOGICAL ABSTRACTS INC.(R)

=> d que l26
L2            3 SEA FILE=REGISTRY ABB=ON  PLU=ON  9002-93-1 OR 9002-92-0 OR
                9005-65-6
L3         4779 SEA FILE=BIOSIS ABB=ON  PLU=ON  L2
L4        22438 SEA FILE=BIOSIS ABB=ON  PLU=ON  TRITON OR TWEEN
L5         4780 SEA FILE=BIOSIS ABB=ON  PLU=ON  (INFLUENZ?/TI,ST (S) VACCIN?/TI
                ,ST)
L6           25 SEA FILE=BIOSIS ABB=ON  PLU=ON  L5 AND (L3 OR L4)
L7        23074 SEA FILE=BIOSIS ABB=ON  PLU=ON  SPLIT
L8          165 SEA FILE=BIOSIS ABB=ON  PLU=ON  L5 AND L7
L9           17 SEA FILE=BIOSIS ABB=ON  PLU=ON  L8 AND (L3 OR L4)
L10          17 SEA FILE=BIOSIS ABB=ON  PLU=ON  L6 AND SPLIT
L11           1 SEA FILE=BIOSIS ABB=ON  PLU=ON  L8 AND SURFACTANT?
L12          18 SEA FILE=BIOSIS ABB=ON  PLU=ON  L9 OR L10 OR L11
L13        3986 SEA FILE=MEDLINE ABB=ON  PLU=ON  L2
L14        6104 SEA FILE=MEDLINE ABB=ON  PLU=ON  INFLUENZA VACCINE/CT
L15       17257 SEA FILE=MEDLINE ABB=ON  PLU=ON  ORTHOMYXOVIRIDAE+NT/CT
L16        5613 SEA FILE=MEDLINE ABB=ON  PLU=ON  VACCINES, ATTENUATED+NT/CT
L17       13534 SEA FILE=MEDLINE ABB=ON  PLU=ON  VIRAL VACCINES/CT
L18         748 SEA FILE=MEDLINE ABB=ON  PLU=ON  L15 AND (L16 OR L17)
L19        4547 SEA FILE=MEDLINE ABB=ON  PLU=ON  L14/MAJ
L20       60023 SEA FILE=MEDLINE ABB=ON  PLU=ON  SURFACE"-"ACTIVE AGENTS+NT/CT

L21           8 SEA FILE=MEDLINE ABB=ON  PLU=ON  L18 AND L20
L22          47 SEA FILE=MEDLINE ABB=ON  PLU=ON  L19 AND L20
L23           3 SEA FILE=MEDLINE ABB=ON  PLU=ON  L19 AND L13
L24          11 SEA FILE=MEDLINE ABB=ON  PLU=ON  L22 AND SPLIT
L25          19 SEA FILE=MEDLINE ABB=ON  PLU=ON  L24 OR L23 OR L21
L26          32 DUP REM L25 L12 (5 DUPLICATES REMOVED)


=> d bib ab ct l=32
UNITS CONVERSION IS NOT AVAILABLE IN THE CURRENT FILE

=> d bib ab ct 1-32

L26  ANSWER 1 OF 32  BIOSIS  COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN   2003:324099  BIOSIS
```

DN PREV200300324099
TI Evaluation of novel aerosol formulations designed for mucosal **vaccination** against **influenza** virus.
AU Smith, Dan J.; Bot, Simona; Dellamary, Luis; Bot, Adrian [Reprint Author]
CS MannKind Corp., 28903 North Avenue Paine, Valencia, CA, 91355, USA abot@mannkindcorp.com
SO Vaccine, (20 June 2003) Vol. 21, No. 21-22, pp. 2805-2812. print. ISSN: 0264-410X (ISSN print).
DT Article
LA English
ED Entered STN: 16 Jul 2003
Last Updated on STN: 16 Jul 2003
AB Influenza viruses are among the most significant human pathogens, responsible for increased seasonal morbidity and mortality particularly in immunodepressed and chronically ill. Conventional vaccination with non-replicative vaccine is currently performed by injection. In the present study, we explore simple spray-dried lipid formulations containing whole inactivated virus or **split**-subunit vaccine that allow aerosolization and thus, mucosal vaccination of the pulmonary tract. We show that by using biocompatible excipients already approved for human use, one could engineer microparticles that induce substantial local and systemic immunity subsequent to pulmonary administration. Exposure of the bronchial-associated lymphoid tissue (BALT) to vaccine was more effective than parenteral or nasal administration in triggering specific immunity. Co-formulation of a biocompatible **surfactant** detergent greatly ameliorated the immune profile of microparticles containing a whole inactivated virus vaccine. In addition, mere formulation of a licensed **split**-subunit vaccine significantly enhanced its immunogenicity. Together, our data underline a simple strategy to convert conventional parenteral vaccination of currently available non-replicative vaccines against influenza virus, into one that is more effective and practical upon respiratory administration.
IT Major Concepts
Immune System (Chemical Coordination and Homeostasis); Infection; Pharmacology; Respiratory System (Respiration)
IT Parts, Structures, & Systems of Organisms
bronchial-associated lymphoid tissue: immune system, respiratory system
IT Diseases
influenza: respiratory system disease, viral disease
Influenza (MeSH)
IT Chemicals & Biochemicals
influenza virus vaccine: immunologic-drug, immunostimulant-drug, aerosol formulation

L26 ANSWER 2 OF 32 MEDLINE on STN
AN 2001409124 MEDLINE
DN 21157789 PubMed ID: 11257408
TI The adjuvanted influenza vaccines with novel adjuvants: experience with the MF59-adjuvanted vaccine.
AU Podda A
CS Clinical Research and Medical Affairs, Chiron Vaccines, Chiron SpA, Via Florentina 1, 53100, Siena, Italy.. audino_podda@chiron.it
SO VACCINE, (2001 Mar 21) 19 (17-19) 2673-80.
Journal code: 8406899. ISSN: 0264-410X.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
(META-ANALYSIS)
LA English
FS Priority Journals
EM 200107

ED Entered STN: 20010723
Last Updated on STN: 20010723
Entered Medline: 20010719

AB Elderly people and subjects with underlying chronic diseases are at increased risk for influenza and related complications. Conventional influenza vaccines provide only limited protection in the elderly population. In order to enhance the immune response to influenza vaccines, several adjuvants have been evaluated. Among these, an oil in water adjuvant emulsion containing squalene, MF59, has been combined with subunit influenza antigens and tested in clinical trials in comparison with non-adjuvanted conventional vaccines. Data from a clinical database of over 10000 elderly subjects immunised with this adjuvanted vaccine (Fluad, Chiron Vaccines, Siena, Italy) demonstrate that, although common postimmunisation reactions are more frequent in recipients of the adjuvanted vaccine, this vaccine is well tolerated, also after re-immunisation in subsequent influenza seasons. Immunogenicity analyses demonstrate a consistently higher immune response with statistically significant increases of postimmunisation geometric mean titres, and of seroconversion and seroprotection rates compared to non-adjuvanted subunit and **split** influenza vaccines, particularly for the A/H3N2 and the B strains. The higher immunogenicity profile of the MF59-adjuvanted vaccine is maintained also after subsequent immunisations. An even higher adjuvant effect was shown in subjects with low pre-immunisation titre and in those affected by chronic underlying diseases. In conclusion, the addition of MF59 to subunit influenza vaccines enhances significantly the immune response in elderly subjects without causing clinically important changes in the safety profile of the influenza vaccine.

CT Check Tags: Female; Human; Male
*Adjuvants, Immunologic: AD, administration & dosage
Adjuvants, Immunologic: AE, adverse effects
Aged
Antibodies, Viral: BL, blood
Databases, Factual
Emulsions
Influenza: IM, immunology
Influenza: PC, prevention & control
***Influenza Vaccine: AD, administration & dosage**
Influenza Vaccine: AE, adverse effects
Italy
***Polysorbates: AD, administration & dosage**
Polysorbates: AE, adverse effects
Safety
*Squalene: AD, administration & dosage
Squalene: AE, adverse effects

L26 ANSWER 3 OF 32 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 2001:42003 BIOSIS
DN PREV200100042003
TI Safety and immunogenicity of a paediatric presentation of an **influenza vaccine.**
AU Gonzalez, M.; Pirez, M. C.; Ward, E.; Dibarboure, H.; Garcia, A. [Reprint author]; Picolet, H.
CS Aventis Pasteur International, 2, Avenue Pont Pasteur, 69007, Lyon, France
SO Archives of Disease in Childhood, (December, 2000) Vol. 83, No. 6, pp. 488-491. print.
CODEN: ADCHAK. ISSN: 0003-9888.
DT Article
LA English
ED Entered STN: 17 Jan 2001
Last Updated on STN: 12 Feb 2002

AB Background: Flu vaccination in otherwise healthy infants and young children is important to prevent severe disease, as well as to control epidemic spread of influenza infection. Aims: To examine the safety and immunogenicity of a paediatric presentation of a purified, inactivated, **triton split** influenza vaccine. Methods: Two doses of the vaccine, provided in prefilled syringes of 0.25 ml, were administered, one month apart, to 67 children under 3 years of age. Results: Nine cases of immediate reaction to vaccination (macules/papules) were observed after the second injection only. During the study period, 9% of children experienced at least one delayed local reaction, and 28% of children presented at least one systemic reaction. Almost all reactions were mild and transient. Immunogenicity results surpassed the European Community recommendations for a 0.50 ml dose of vaccine in adults. Conclusion: This paediatric formulation of inactivated flu vaccine appears safe and immunogenic in children from 6 months to 3 years of age; the convenient presentation in a prefilled syringe of 0.25 ml volume will facilitate administration of the dose recommended for young children.

IT Major Concepts
Infection; Clinical Immunology (Human Medicine, Medical Sciences); Pediatrics (Human Medicine, Medical Sciences); Pulmonary Medicine (Human Medicine, Medical Sciences)

IT Diseases
influenza infection: respiratory system disease, viral disease
Influenza (MeSH)

L26 ANSWER 4 OF 32 MEDLINE on STN
AN 2000492027 MEDLINE
DN 20340125 PubMed ID: 10885616
TI A TritonX-100-**split** virion influenza vaccine is safe and fulfills the committee for proprietary medicinal products (CPMP) recommendations for the European Community for Immunogenicity, in Children, Adults and the Elderly.
AU Lina B; Fletcher M A; Valette M; Saliou P; Aymard M
CS Laboratoire de Virologie, Centre National de Reference de la Grippe (France Sud), Faculte de Medecine Lyon Grange Blanche, France.
SO BIOLOGICALS, (2000 Jun) 28 (2) 95-103.
Journal code: 9004494. ISSN: 1045-1056.
CY ENGLAND: United Kingdom
DT (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200010
ED Entered STN: 20001027
Last Updated on STN: 20001027
Entered Medline: 20001019
AB Influenza epidemics are an important cause of morbidity and mortality throughout the world. Current recommendations from Health Authorities emphasize annual immunization of people who are particularly at risk from an influenza virus infection; however, vaccination of working adults and of school children also has been shown to provide public health benefits. To give it a more advantageous reactogenicity profile than the diethylether-**split** influenza vaccines available previously, a **split** virion influenza vaccine has been produced with TritonX-100. In a series of clinical trials, Aventis Pasteur (formerly, Pasteur Merieux Connaught) tested both the safety and immunogenicity of this TritonX-100-**split** virion influenza vaccine in 566 subjects (42 children, 296 adults, and 228 elderly adults) during three influenza seasons (1991, 1993, and 1995). The TritonX-100-**split** virion vaccine was well tolerated: no serious adverse events were recorded during the 21 days

following immunization. Among the local reactions observed, mild pain, redness, or induration at the injection site were the most frequently reported. Fever (38.0 to 38.5 degrees C) was noted in five adults or elderly subjects (1%), and in two children (5%). Immunogenicity was determined by measuring serum haemagglutinin antibody titres specific to each vaccine virus strain. In each of the three vaccination campaigns, the TritonX-100-**split** virion influenza vaccine fulfilled the Notes for Guidance on Harmonization of Requirements for Influenza Vaccines outlined by the Committee for Proprietary Medicinal Products (CPMP) of the European Community for an influenza virus vaccine (i.e., seroprotection, seroconversion, or increase of geometric mean titre) in all age groups.

CT Check Tags: Animal; Comparative Study; Human
Adolescent
Adult
Aged
Aged, 80 and over
Antibodies, Viral: BI, biosynthesis
Antigens, Viral: IM, immunology
Chick Embryo
Child
***Detergents: PD, pharmacology**
Hemagglutinin Glycoproteins, Influenza Virus: IM, immunology
*Influenza A Virus, Human: DE, drug effects
Influenza A Virus, Human: IM, immunology
*Influenza B virus: DE, drug effects
Influenza B virus: IM, immunology
Influenza Vaccine: AE, adverse effects
Influenza Vaccine: IM, immunology
***Influenza Vaccine: ST, standards**
Middle Age
***Octoxynol: PD, pharmacology**
Safety
Vaccination: AE, adverse effects
*Virion: DE, drug effects

L26 ANSWER 5 OF 32 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 1997:460286 BIOSIS
DN PREV199799759489
TI Determination of **triton** X-100 in **influenza vaccine** by high-performance liquid chromatography and capillary electrophoresis.
AU Heinig, Katja; Vogt, Carla [Reprint author]
CS Univ. Leipzig, Dep. Chem. Mineral., Inst. Analytical Chem., Linnestrasse 3, D-04103 Leipzig, Germany
SO Fresenius' Journal of Analytical Chemistry, (1997) Vol. 359, No. 2, pp. 202-206.
CODEN: FJACES. ISSN: 0937-0633.
DT Article
LA English
ED Entered STN: 27 Oct 1997
Last Updated on STN: 27 Oct 1997
AB **Triton** X-100 is applied to influenza vaccines at different stages of the manufacturing process to prevent aggregation and precipitation of biomolecules. Furthermore it is used to disintegrate the virus particles in **split** vaccine and to guarantee the homogeneity during production and utilisation. The final concentration of **Triton** X-100 has to be determined because the concentration changes in manufacturing process. The determination of the total amount of **Triton** X- 100 as well as the separation of its ethylene oxide oligomers was possible with high performance liquid chromatography (HPLC)

and capillary electrophoresis (CE). In HPLC a change of the column and eluent was necessary, in CE different electrolytes were used for the various separation effects. The HPLC method for the analysis of total **Triton** was preferred for the quantification of **Triton** X-100 in influenza vaccine because of better linearity, reproducibility and detection sensitivity compared to CE. In the end products an average concentration of 0.117 mg/mL was found.

IT Major Concepts
Biochemistry and Molecular Biophysics; Methods and Techniques; Pharmacology

IT Chemicals & Biochemicals
TRITON

L26 ANSWER 6 OF 32 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 1996:259940 BIOSIS
DN PREV199698816069
TI Safety and immunogenicity of an inactivated **triton split influenza vaccine** in different groups of age.
AU Lina, B. [Reprint author]; Valette, M. [Reprint author]; Picolet, H.; Saliou, P.; Aymard, M. [Reprint author]
CS Lab. Virologie, Centre Natl. Reference Grippe, Fac. Med., Lyon Grange Blanche, Lyon, France
SO Abstracts of the General Meeting of the American Society for Microbiology, (1996) Vol. 96, No. 0, pp. 273.
Meeting Info.: 96th General Meeting of the American Society for Microbiology. New Orleans, Louisiana, USA. May 19-23, 1996.
ISSN: 1060-2011.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 31 May 1996
Last Updated on STN: 31 May 1996
IT Major Concepts
Blood and Lymphatics (Transport and Circulation); Epidemiology (Population Studies); Immune System (Chemical Coordination and Homeostasis); Infection; Metabolism; Microbiology; Pharmacology; Public Health (Allied Medical Sciences)
IT Chemicals & Biochemicals
TRITON

L26 ANSWER 7 OF 32 MEDLINE on STN
AN 96043088 MEDLINE
DN 96043088 PubMed ID: 7474883
TI Comparison of the effects of five adjuvants on the antibody response to influenza virus antigen in guinea pigs.
AU Robuccio J A; Griffith J W; Chroscinski E A; Cross P J; Light T E; Lang C M
CS Wyeth-Ayerst Laboratories, Marietta, PA 17547, USA.
SO LABORATORY ANIMAL SCIENCE, (1995 Aug) 45 (4) 420-6.
Journal code: 1266503. ISSN: 0023-6764.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199512
ED Entered STN: 19960124
Last Updated on STN: 19960124
Entered Medline: 19951207
AB Five adjuvants were tested for their effect on the immune response in guinea pigs to the hemagglutinin antigen of influenza virus strain

B/Panama. Vaccines containing 924 micrograms of hemagglutinin antigen/ml were prepared at high and low doses of Freund's complete and incomplete adjuvants, Syntex adjuvant, RIBI's adjuvant, TiterMax adjuvant, and aluminum phosphate adjuvant. Responses to these vaccines were compared with those to a control vaccine containing influenza virus B/Panama hemagglutinin antigen and saline. On day 28, vaccines containing the following adjuvant doses had significantly higher titers than the titer for the control: Freund adjuvants at high and low doses, RIBI at high dose, TiterMax at high and low doses, and aluminum phosphate at high dose. On day 42, vaccines containing the following adjuvant doses had significantly higher titers than that for the control: Freund adjuvants at high and low doses, RIBI at high dose, TiterMax at high dose, and aluminum phosphate at high dose. Freund adjuvants at high and low doses, RIBI adjuvant at high dose, and aluminum phosphate at high dose caused significantly greater swelling at the inoculation site than did the control vaccine. TiterMax adjuvant at high and low doses, and aluminum phosphate at low dose caused minor swelling at the inoculation site, but it was not significantly different from the swelling caused by the control vaccine. Syntex adjuvant at high and low doses, RIBI at low dose, and control (saline/antigen) at high and low doses caused no swelling after inoculation. Overall, the high dose of adjuvants caused greater tissue swelling than did the low dose of adjuvants.(ABSTRACT TRUNCATED AT 250 WORDS)

CT Check Tags: Animal; Comparative Study; Male
Acetylmuramyl-Alanyl-Isoglutamine: AE, adverse effects
Acetylmuramyl-Alanyl-Isoglutamine: AA, analogs & derivatives
Acetylmuramyl-Alanyl-Isoglutamine: PD, pharmacology
Adjuvants, Immunologic: AD, administration & dosage
Adjuvants, Immunologic: AE, adverse effects
*Adjuvants, Immunologic: PD, pharmacology
Aluminum Compounds: AE, adverse effects
Aluminum Compounds: PD, pharmacology
*Antibodies, Viral: BL, blood
*Antigens, Viral: IM, immunology
Cell Wall Skeleton: AE, adverse effects
Cell Wall Skeleton: PD, pharmacology
Cord Factors: AE, adverse effects
Cord Factors: PD, pharmacology
Freund's Adjuvant: AE, adverse effects
Freund's Adjuvant: PD, pharmacology
*Guinea Pigs: IM, immunology
Hemagglutinin Glycoproteins, Influenza Virus
*Hemagglutinins, Viral: IM, immunology
***Influenza B virus: IM, immunology**
Lipid A: AE, adverse effects
Lipid A: AA, analogs & derivatives
Lipid A: PD, pharmacology
Phosphates: AE, adverse effects
Phosphates: PD, pharmacology
Poloxalene: AE, adverse effects
Poloxalene: PD, pharmacology
Polysorbates: AE, adverse effects
Polysorbates: PD, pharmacology
Squalene: AE, adverse effects
Squalene: AA, analogs & derivatives
Squalene: PD, pharmacology
Viral Envelope Proteins: IM, immunology
Viral Vaccines: IM, immunology

L26 ANSWER 8 OF 32 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

AN 1995:526095 BIOSIS
DN PREV199598540395
TI Use of **Triton** X-100 as **split** agent in the **influenza vaccine**: Evaluation of the immunogenicity and safety in elderly population.
AU Bodenan, L.; Sliosberg, R.; De La Forest Divonne, F.; Arassus, L.; Le Cam, N.
CS Saint Germain en Laye Hosp., Pasteur Merieux, France
SO Abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy, (1995) Vol. 35, No. 0, pp. 188.
Meeting Info.: 35th Interscience Conference on Antimicrobial Agents and Chemotherapy. San Francisco, California, USA. September 17-20, 1995.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LA English
ED Entered STN: 5 Dec 1995
Last Updated on STN: 6 Dec 1995
IT Major Concepts
Clinical Endocrinology (Human Medicine, Medical Sciences); Geriatrics (Human Medicine, Medical Sciences); Immune System (Chemical Coordination and Homeostasis); Infection; Pharmacology; Toxicology
IT Chemicals & Biochemicals
TRITON X-100

L26 ANSWER 9 OF 32 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 1992:517712 BIOSIS
DN PREV199243115162; BR43:115162
TI SAFETY AND IMMUNOGENICITY OF A NEW **TRITON** X-100 **SPLIT INFLUENZA VACCINE.**
AU JULIEN H [Reprint author]; MAYAUDON J L; MARIE F N; LE CAM N
CS FRENCH FIRE BRIGADE, BOUCICAUT HOSPITAL, PASTEUR MERIEUX, PARIS, FR
SO Program and Abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy, (1992) Vol. 32, pp. 162.
Meeting Info.: 32ND INTERSCIENCE CONFERENCE ON ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, ANAHEIM, CALIFORNIA, USA, OCTOBER 11-14, 1992. PROGRAM ABSTR INTERSCI CONF ANTIMICROB AGENTS CHEMOTHERAPY.
ISSN: 0733-6373.
DT Conference; (Meeting)
FS BR
LA ENGLISH
ED Entered STN: 11 Nov 1992
Last Updated on STN: 12 Nov 1992
IT Major Concepts
Immune System (Chemical Coordination and Homeostasis); Infection; Pharmacology

L26 ANSWER 10 OF 32 MEDLINE on STN
AN 90150676 MEDLINE
DN 90150676 PubMed ID: 2302839
TI Specificity and in vitro transfer of the immunosuppressive effect of detergent-disrupted influenza virus vaccine.
AU Smith T L; Jennings R
CS Department of Virology, University of Sheffield Medical School, Sheffield, England.
SO CLINICAL AND EXPERIMENTAL IMMUNOLOGY, (1990 Jan) 79 (1) 87-94.
Journal code: 0057202. ISSN: 0009-9104.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English

FS Priority Journals
EM 199003
ED Entered STN: 19900601
Last Updated on STN: 19900601
Entered Medline: 19900328
AB Primed murine splenocytes give an in vitro antibody response to influenza whole virus vaccine (WVV), as measured by enzyme immunoassay (EIA). When subunit vaccine (SV) of either influenza A or influenza B virus was added to in vitro splenocyte cultures stimulated with WVV, the EIA antibody response to homologous WVV was reduced. This reduction in antibody response was observed when SV was prepared using zwitterionic detergent (empigen BB), non-ionic detergent (triton-X-100) or cationic detergent cetyl-trimethyl ammonium bromide (CTAB); it was found to be effected only by SV of strains of the same virus subtype--when SVs prepared from a heterotypic (H3N2) strain, an H1N1 strain and an influenza B strain were added to splenocyte cultures in the presence of WVV. When splenocytes from immunologically naive mice, exposed in vitro to SV, were transferred to secondary cultures of primed splenocytes, the antibody response to WVV in the secondary cultures was also reduced. Mechanisms that may suppress the in vitro antibody response are discussed.
CT Check Tags: Animal; Female
*Antibodies, Viral: BI, biosynthesis
*Antibody Specificity
Cells, Cultured
Cetrimonium Compounds
Detergents
*Immunosuppression
***Influenza Vaccine: IM, immunology**
Mice
Mice, Inbred BALB C
Octoxynol
Polyethylene Glycols
Spleen: IM, immunology

L26 ANSWER 11 OF 32 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 1989:181887 BIOSIS
DN PREV198987093153; BA87:93153
TI IMPROVED COLORIMETRIC ASSAY FOR DETECTING **INFLUENZA** B VIRUS NEUTRALIZING ANTIBODY RESPONSES TO **VACCINATION** AND INFECTION.
AU TANNOCK G A [Reprint author]; PAUL J A; HERD R; BARRY R D; REID A L A; HENSLEY M J; GILLETT R S; GILLETT S M; LAWRANCE P; ET AL
CS FAC MED, UNIV NEWCASTLE, NEWCASTLE, NEW SOUTH WALES, 2308 AUSTRALIA
SO Journal of Clinical Microbiology, (1989) Vol. 27, No. 3, pp. 524-528. CODEN: JCMIDW. ISSN: 0095-1137.
DT Article
FS BA
LA ENGLISH
ED Entered STN: 9 Apr 1989
Last Updated on STN: 9 Apr 1989
AB An automated neutralization test for influenza B virus is described in which antibody titers are determined according to the release of neutral red for infected or uninfected cells of the Madin-Darby canine kidney line. Endpoints are determined in a standard enzyme-linked immunosorbent assay reader. The test requires no expensive immunologic reagents and was used to evaluate responses to both vaccination and natural infection against influenza B virus. Overall responses to vaccination were comparable with those obtained by hemagglutination inhibition, using **Tween**-ether-**split** influenza B/Ann Arbor/1/86 virus as the antigen (the HI-TE test). The sensitivities of neutralization responses compared with those obtained by the HI-TE test for two vaccines

were 88 and 89%; the specificities were lower at 61 and 60%, respectively. Responses to vaccination, measured by hemagglutination inhibition, were significantly higher with **split** virus compared with whole virus. However, seroconversion by both the HI-TE and neutralization tests was observed in 5 of 10 individuals from whom virus was detected by either culture of nasal or throat washings or the presence of antigen from immunofluorescence in cells from nasal washings.

IT Major Concepts
Immune System (Chemical Coordination and Homeostasis); Infection; Pharmacology; Pulmonary Medicine (Human Medicine, Medical Sciences); Serology (Allied Medical Sciences)

L26 ANSWER 12 OF 32 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 1989:335313 BIOSIS
DN PREV198988038313; BA88:38313
TI **INFLUENZA VACCINE** AND THEOPHYLLINE METABOLISM IS THERE AN INTERACTION.
AU BRYETT K A [Reprint author]; LEVY J; PARIENTE R; GOBERT P; FALQUET J C V
CS MERIEUX, UK CLIVEMONT HOUSE, CLIVEMONT ROAD, MAIDENHEAD SL6 7BU, UK
SO Acta Therapeutica, (1989) Vol. 15, No. 1, pp. 49-58.
CODEN: ACTTDZ. ISSN: 0378-0619.
DT Article
FS BA
LA ENGLISH
ED Entered STN: 20 Jul 1989
Last Updated on STN: 26 Aug 1989
AB Nine volunteers receiving continuous theophylline therapy were studied in detail after receiving influenza vaccination with a **tween** ether **split** virion vaccine (Merieux). Using clinical, physiological and biochemical parameters, no alteration in theophylline metabolism was observed in any volunteer. A critical review of the published literature on this subject shows that the impression that influenza vaccination alters theophylline metabolism is based on work involving only four subjects, three of whom may have had a comitant viral infection which is known to alter metabolism. Subsequently a number of well controlled studies have all failed to find any evidence of an interaction between theophylline and influenza vaccination. Patients requiring theophylline treatment are, by the nature of their disease, at risk from influenza and from the effects on drug metabolism of the natural disease. There are no significant data to contraindicate influenza vaccination in this group.
IT Major Concepts
Immune System (Chemical Coordination and Homeostasis); Infection; Metabolism; Pharmacology; Pulmonary Medicine (Human Medicine, Medical Sciences)

L26 ANSWER 13 OF 32 MEDLINE on STN
AN 87139946 MEDLINE
DN 87139946 PubMed ID: 3819697
TI Demonstration of an immunosuppressive action of detergent-disrupted influenza virus on the antibody response to inactivated whole virus vaccine.
AU Jennings R; Pemberton R M; Smith T L; Amin T; Potter C W
SO JOURNAL OF GENERAL VIROLOGY, (1987 Feb) 68 (Pt 2) 441-50.
Journal code: 0077340. ISSN: 0022-1317.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198704
ED Entered STN: 19900303

Last Updated on STN: 19900303
Entered Medline: 19870401

AB In a series of experiments performed in hamsters and mice, administration of mixtures of detergent-disrupted (SV) influenza A X49 (H3N2) virus and inactivated X49 whole virus (WV) vaccine induced lower serum antibody titres than equivalent or lower doses of WV vaccine alone. This reduction in antibody titre was also observed using influenza A (H1N1) and influenza B (B/Hong Kong/8/73) SV and WV vaccine preparations. The results suggested that SV preparations can suppress the serum antibody response to WV vaccine. A suppressive effect of SV influenza virus on WV vaccine was also observed in an in vitro antibody-forming system, using primed mouse spleen cells. In this system, SV induced markedly lower IgG and IgM antibody responses than WV vaccine, and mixtures of SV with WV reproducibly resulted in lowered antibody responses compared to those elicited by WV alone. Possible reasons for these findings are discussed in the light of the known low immunogenicity observed for split and subunit influenza virus vaccine preparations in animals and in unprimed human populations.

CT Check Tags: Animal; Comparative Study; Female; Support, Non-U.S. Gov't
*Antibodies, Viral: BI, biosynthesis
Cells, Cultured
***Detergents: PD, pharmacology**
Hamsters
Immune Tolerance
Immunoglobulin G: BI, biosynthesis
Immunoglobulin M: BI, biosynthesis
Mesocricetus
Mice
Mice, Inbred BALB C
***Orthomyxoviridae: DE, drug effects**
Orthomyxoviridae: IM, immunology
Spleen: CY, cytology
***Surface-Active Agents: PD, pharmacology**
Vaccines, Attenuated: IM, immunology
***Viral Vaccines: IM, immunology**

L26 ANSWER 14 OF 32 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 1987:105455 BIOSIS
DN PREV198783054433; BA83:54433
TI EVALUATION OF THE EFFICACY OF **SPLIT**-PRODUCT TRIVALENT AH1N1 AH3N2 AND B **INFLUENZA VACCINES** PROTECTIVE EFFICACY.
AU OCHIAI H [Reprint author]; SHIBATA M; KAMIMURA K; NIWAYAMA S
CS DEP OF VIROL, TOYAMA MED AND PHARMACEUTICAL UNIV, TOYAMA, TOYAMA 930-01
SO Microbiology and Immunology, (1986) Vol. 30, No. 11, pp. 1151-1166.
CODEN: MIIMDV. ISSN: 0385-5600.
DT Article
FS BA
LA ENGLISH
ED Entered STN: 26 Feb 1987
Last Updated on STN: 26 Feb 1987

AB A total of 1,995 primary school children (1,461 vaccinees and 531 non-vaccinees) were studied to evaluate the protective efficacy of **Tween**-ether **split** trivalent A(H1N1), A(H3N2), and B influenza vaccines by comparison of the incidence of confirmed infection in two groups during 1980 to 1981. During the study period, epidemics caused by antigenically different influenza viruses, that is A(H1N1) epidemics in 1981 and 1984, a B epidemic in 1982 and an A(H3N2) epidemic in 1983, were experienced, and at the same time strains changed by antigenic drift were frequently isolated. In these epidemics, 61% to 87% of the children reported respiratory illnesses and 18% to 48% of the

illness were influenza confirmed by seroconversion. Throughout these four epidemics, the incidence of confirmed infection among the vaccinees (7.8% to 33.8%) was 6.5% to 34.8% lower than that among the nonvaccinees (35.4% to 51.6%), demonstrating that the vaccine was effective ($\chi 2$ = 76.34, P < 0.001). However, this effectiveness was not seen in an epidemic in one of the entrant schools in 1984, possibly caused by a strain with intense antigenic drift. On the basis of data on incidence of various symptoms, duration of fever and the number of days of absence from class, it was considered that clinical symptoms in the vaccinees were milder than those in the nonvaccinees. When the titers of hemagglutination-inhibiting (HAI) antibody against the vaccine strains were measured, the protective level of HAI antibody giving ≤ 50% incidence of infection was 1:64, but it increased to 1:256 in the 1984 epidemic, reflecting the high rate of isolates with intense antigenic drift.

IT Major Concepts
Immune System (Chemical Coordination and Homeostasis); Infection; Metabolism; Pathology; Pediatrics (Human Medicine, Medical Sciences); Pharmacology; Pulmonary Medicine (Human Medicine, Medical Sciences)

L26 ANSWER 15 OF 32 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 1987:105456 BIOSIS
DN PREV198783054434; BA83:54434
TI EVALUATION OF THE EFFICACY OF **SPLIT**-PRODUCT TRIVALENT A H1N1 AH3N2 AND B **INFLUENZA VACCINES** REACTOGENICITY IMMUNOGENICITY AND PERSISTENCE OF ANTIBODIES FOLLOWING TWO DOSES OF **VACCINES.**
AU OCHIAI H [Reprint author]; SHIBATA M; KAMIMURA K; NIWAYAMA S
CS DEP OF VIROL, TOYAMA MED AND PHARMACEUTICAL UNIV TOYAMA, TOYAMA 930-01
SO Microbiology and Immunology, (1986) Vol. 30, No. 11, pp. 1141-1150. CODEN: MIIMDV. ISSN: 0385-5600.
DT Article
FS BA
LA ENGLISH
ED Entered STN: 26 Feb 1987
Last Updated on STN: 26 Feb 1987
AB The reactogenicity and immunogenicity of **Tween**-ether **split** trivalent A(H1N1), A(H3N2), and B influenza vaccine in primary school children aged seven to 12 years, and the persistence of antibodies following two doses of vaccine were studied during 1980-1984. Adverse reactions were infrequent, and, even when reported, were chiefly local ones, mild in nature and of short duration. Most of the reactions were less frequent after the second dose than after the first dose. Most of the systemic reactions occurred during the intervaccination period with almost equal frequency, indicating that careful consideration is required to judge whether they were induced by vaccination or not. This vaccine had induced adequate hemagglutination inhibiting (HAI) antibody because the geometric mean titers (GMTs) of the vaccinees were two- to eightfold higher than those of the nonvaccinees to any of the vaccine antigens following two doses of vaccine. In general, the responses to A(H3N2) virus were the best among the vaccine antigens through the four vaccination seasons, but there was a tendency to show a poorer response to the same type (or subtype) of virus antigen as the causative one during a protracted epidemic. The antibodies induced by either vaccination or natural infection were shown to persist for less than a year, supporting the recommendation for annual vaccination.
IT Major Concepts
Immune System (Chemical Coordination and Homeostasis); Infection; Metabolism; Pediatrics (Human Medicine, Medical Sciences); Pharmacology; Pulmonary Medicine (Human Medicine, Medical Sciences)

L26 ANSWER 16 OF 32 MEDLINE on STN DUPLICATE 1
AN 86046494 MEDLINE
DN 86046494 PubMed ID: 3933204
TI Quantification of haemagglutinin of influenza Tween-ether **split** vaccines by immunodiffusion.
AU Johannsen R; Moser H; Hinz J; Friesen H J; Gruschkau H
SO VACCINE, (1985 Sep) 3 (3 Suppl) 235-40.
Journal code: 8406899. ISSN: 0264-410X.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198512
ED Entered STN: 19900321
Last Updated on STN: 19900321
Entered Medline: 19851213
AB The haemagglutinin content of monovalent influenza whole virus and Tween-ether **split** vaccines derived therefrom, were assayed comparatively using single radial immunodiffusion (SRID, the only test recommended for influenza vaccines by the European Pharmacopoeia Commission), quantitative SDS-polyacrylamide gel electrophoresis and immunization of guinea pigs. If SRID was performed with **split** vaccines, reduced haemagglutinin values were consistently recorded which were 50-25% of values obtained before disruption of virions. If, however, disruption was conducted in the presence of excess detergent thus preventing aggregate formation of solubilized haemagglutinin, test values comparable to those of whole virus vaccines were obtained. In agreement with these results, immunization experiments revealed that whole virus and the corresponding **split** vaccines exhibited comparable immunogenicity in guinea pigs. From SDS-polyacrylamide gel electrophoresis and densitometer tracings obtained by scanning the gels after staining with either Coomassie Blue or fluorescein isothiocyanate-labelled concanavalin A it was calculated that about 90% of whole virus HA2 was recovered in Tween-ether **split** vaccines. From our experiments we conclude that precise quantification of solubilized haemagglutinin is not achievable by the single radial immunodiffusion test alone. Aggregate formation of solubilized haemagglutinin frequently occurs when the applied detergent is removed and, therefore, a physico-chemical method including an effective disaggregation procedure like SDS treatment in combination with PAGE is recommended.
CT Check Tags: Animal; Comparative Study
Antibodies, Viral: BI, biosynthesis
Electrophoresis, Polyacrylamide Gel
Ether, Ethyl
Guinea Pigs
*Hemagglutinins, Viral: AN, analysis
Immunization
Immunodiffusion
***Influenza Vaccine: AN, analysis**
Influenza Vaccine: IM, immunology
Influenza Vaccine: IP, isolation & purification
Polysorbates
Sodium Dodecyl Sulfate

L26 ANSWER 17 OF 32 MEDLINE on STN
AN 86046707 MEDLINE
DN 86046707 PubMed ID: 4060954
TI [Immune response of noninbred mice to subvirion influenza vaccines with various antigen and sorbent loads].

Izuchenie immunnogo otveta neinbrednykh myshei na subvirionnye gripkoznye vaktsiny s var'iruemoi nagruzkoi antigena i sorbenta.
AU Evdokimova I V; Zhukova T Ia; Shapiro N I
SO ZHURNAL MIKROBIOLOGII, EPIDEMIOLOGII I IMMUNOBIOLOGII, (1985 Aug) (8) 51-4.
Journal code: 0415217. ISSN: 0372-9311.
CY USSR
DT Journal; Article; (JOURNAL ARTICLE)
LA Russian
FS Priority Journals
EM 198512
ED Entered STN: 19900321
Last Updated on STN: 19970203
Entered Medline: 19851210
AB The variants of splitted and subunit influenza monovaccines from virus strains A/Leningrad/385/80R (H3N2) and A/Kiev/59/79R (H1N1), adsorbed on aluminium hydroxide and having the varying content of hemogglutinin and the carrier, have been studied. The immune response of noninbred mice to a single and double injections of these vaccines have been evaluated, the concentrations of the antigen and the carrier inducing a high response in the animals, have been determined. Differences in the immunological potency of hemagglutinins H1 and H3 have been noted.
CT Check Tags: Animal
Aluminum Hydroxide: IM, immunology
*Antigen-Antibody Complex: IM, immunology
*Antigens, Viral: IM, immunology
Dose-Response Relationship, Immunologic
English Abstract
Hemagglutinins, Viral: IM, immunology
***Immunosorbents: IM, immunology**
Influenza A Virus, Human: IM, immunology
*Influenza Vaccine: IM, immunology
Mice
Vaccines, Attenuated: IM, immunology
*Virion: IM, immunology

L26 ANSWER 18 OF 32 MEDLINE on STN
AN 84175715 MEDLINE
DN 84175715 PubMed ID: 6143494
TI Disruption of influenza virus A by diethylether-Tween and tri-N-butyl phosphate-Tween mixtures.
AU Danihelkova H; Zavadova H
SO ACTA VIROLOGICA, (1984 Jan) 28 (1) 26-32.
Journal code: 0370401. ISSN: 0001-723X.
CY Czechoslovakia
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198405
ED Entered STN: 19900319
Last Updated on STN: 19970203
Entered Medline: 19840524
AB In search for optimal conditions of influenza virus A/Brazil/78(H1N1) disruption by diethylether-Tween 80 and tri-n-butyl phosphate (TNBP)-Tween 80 mixtures, the following treatments were found suitable: for 120 min at 4 degrees C with 3.3% TNBP and 0.1% Tween 80 or for 120 min at 4 degrees C with diethylether and 0.1% Tween 80 (ratio of diethylether and treated virus material 1:1). Disruption by TNBP appeared more favourable not only because of the convenient performance but also due to the higher antibody-inducing ability of the product obtained. The suggested removal

of TNBP from the disruption product by extraction into hexan is easy and reliable. Chemical analysis enabled precise detection of 0.1% TNBP in the "vaccine" product. The hexan-extracted "vaccine" contained less than 0.05% TNBP, a concentration non-toxic for mice.

CT Antibodies, Viral: IM, immunology
Hemagglutinins, Viral: IP, isolation & purification
***Influenza A Virus, Human: DE, drug effects**
Influenza A Virus, Human: IM, immunology
Neuraminidase: IP, isolation & purification
***Polysorbates: PD, pharmacology**
Viral Vaccines: IM, immunology

L26 ANSWER 19 OF 32 MEDLINE on STN DUPLICATE 2
AN 84061947 MEDLINE
DN 84061947 PubMed ID: 6417143
TI The quantification of the haemagglutinin content of influenza whole virus and Tween-ether **split** vaccines.
AU Johannsen R; Moser H; Hinz J; Friesen H J; Gruschkau H
SO JOURNAL OF BIOLOGICAL STANDARDIZATION, (1983 Oct) 11 (4) 341-52.
Journal code: 0400335. ISSN: 0092-1157.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198401
ED Entered STN: 19900319
Last Updated on STN: 19900319
Entered Medline: 19840107
AB Monovalent whole virus and Tween-ether **split** vaccines prepared from influenza A/Bangkok, A/Brazil and B/Singapore were assayed for haemagglutinin content using single radial immunodiffusion (SRID), quantitative sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE) and immunization of guinea pigs. When SRID was performed with **split** vaccines, haemagglutinin values were consistently recorded which were in the range of 50 to 25% of the values obtained before disruption of virions. When, however, disruption was conducted in the presence of excess detergent, thus preventing aggregate formation of solubilized haemagglutinin, test values comparable with those of whole virus vaccines were obtained. In agreement with these results, immunization experiments revealed that whole virus and corresponding **split** vaccines exhibited comparable immunogenicity in guinea pigs. Additionally it could be calculated from SDS-PAGE and densitometer tracings, obtained by scanning the gels after staining with either Coomassie blue or FITC-Con A, that 90 to 95% of whole virus HA2 was recovered in Tween-ether **split** vaccines. On the basis of these findings we conclude that precise quantification of Tween-ether **split** vaccines is not possible by the SRID test alone. As aggregate formation of solubilized haemagglutinin occurs, we suggest that either a physico-chemical method including a disaggregation procedure, such as SDS treatment, or immunological evaluation of the original whole virus preparation before disruption of virions should be applied as an additional criterion for quantification of influenza Tween-ether **split** vaccines.
CT Check Tags: Animal
Electrophoresis, Polyacrylamide Gel: MT, methods
Ethers
Guinea Pigs
Hemagglutination Tests
*Hemagglutinins: AN, analysis
Immunodiffusion

***Influenza Vaccine: IM, immunology**
Orthomyxoviridae: DE, drug effects
Polysorbates
Proteins: AN, analysis

L26 ANSWER 20 OF 32 MEDLINE on STN DUPLICATE 3
AN 83071700 MEDLINE
DN 83071700 PubMed ID: 6847954
TI Influenza vaccines in children. Comparison of new cetrimonium bromide and standard ether-treated vaccines.
AU Gross P A; Quinnan G V; Gaerlan P F; Denning C R; Lazicki M; Bernius M
NC 223-80-1102
SO AMERICAN JOURNAL OF DISEASES OF CHILDREN, (1983 Jan) 137 (1) 26-8.
Journal code: 0370471. ISSN: 0002-922X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 198301
ED Entered STN: 19900317
Last Updated on STN: 19900317
Entered Medline: 19830127
AB We compared a new cetrimonium bromide (CTAB) subunit vaccine with a conventional polysorbate (Tween)-ether **split**-product vaccine in 63 children and young adults. The vaccines each contained influenza A/Bangkok/79, A/Brazil/78, B/Singapore/79; two doses were given one month apart. Among persons initially seronegative for A/Bangkok/79, the geometric mean antibody titer rose to more than 100 following one dose of vaccine, while those initially seropositive had titers of greater than 200 after one dose of either vaccine. Neither vaccine was able to induce comparable antibody titers to A/Brazil/78 or B/Singapore/79 after one dose in initially seronegative persons. After two doses the titers were greater than 100 for A/Brazil but not for B/Singapore. An A/Bangkok epidemic struck the New York City metropolitan area. The attack rate in the unvaccinated matched sibling control group was 35% (15/43). Only two of the 27 recipients of cetrimonium bromide vaccine and none of the 36 polysorbate-ether vaccines had a fourfold or greater increase in antibody titer during the epidemic.
CT Check Tags: Comparative Study; Human; Support, U.S. Gov't, P.H.S.
Adult
*Ammonium Compounds
*Cetrimonium Compounds
Cetrimonium Compounds: IM, immunology
Child
Cystic Fibrosis: IM, immunology
Influenza: EP, epidemiology
*Influenza: PC, prevention & control
Influenza Vaccine: IM, immunology
***Influenza Vaccine: TU, therapeutic use**
New York City
Orthomyxoviridae: IM, immunology
***Polysorbates**
Polysorbates: IM, immunology

L26 ANSWER 21 OF 32 MEDLINE on STN
AN 82201915 MEDLINE
DN 82201915 PubMed ID: 7080763
TI [Standards of attenuated influenza vaccine].
Izuchenie standartnosti rasshcheplennoi grippoznoi vaktsiny.
AU Egorov P A; Pushkarev M A; Vasiaev A I; Ishkil'din I B; Veselov S Iu

SO ZHURNAL MIKROBIOLOGII, EPIDEMIOLOGII I IMMUNOBIOLOGII, (1982 Apr) (4) 72-4.
Journal code: 0415217. ISSN: 0372-9311.
CY USSR
DT Journal; Article; (JOURNAL ARTICLE)
LA Russian
FS Priority Journals
EM 198207
ED Entered STN: 19900317
Last Updated on STN: 19970203
Entered Medline: 19820719
AB Adsorbed chemical influenza vaccine is a standard preparation. It meets with the WHO requirements with respect to the content of hemagglutinin, ovalbumin, protein nitrogen. For the dosage of the vaccine by the hemagglutinin content in weight units (microgram) in the process of manufacture, the development of the national standard of this antigen is necessary. After the treatment of virus suspension with ether the number of intact virions remains stable, constituting 3-4%.
CT Check Tags: Comparative Study
Adsorption
Detergents: PD, pharmacology
English Abstract
Ether, Ethyl: PD, pharmacology
Influenza A Virus, Human: DE, drug effects
Influenza A Virus, Human: IM, immunology
Influenza Vaccine: IM, immunology
*Influenza Vaccine: ST, standards
Vaccines, Attenuated: IM, immunology
Vaccines, Attenuated: ST, standards

L26 ANSWER 22 OF 32 MEDLINE on STN
AN 82076120 MEDLINE
DN 82076120 PubMed ID: 7031085
TI Comparison of new triton X-100- and tween-ether-treated **split** -treated vaccines in children.
AU Gross P A; Ennis F A; Gaerlan P F; Denning C R; Setia U; Davis W J; Bisberg D S
NC 223-76-1102
SO JOURNAL OF CLINICAL MICROBIOLOGY, (1981 Nov) 14 (5) 534-8.
Journal code: 7505564. ISSN: 0095-1137.
CY United States
DT (CLINICAL TRIAL)
(CONTROLLED CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198202
ED Entered STN: 19900316
Last Updated on STN: 19980206
Entered Medline: 19820212
AB **Split**-product vaccines (SPVs) combine the desirable properties of no systemic reactogenicity and adequate immunogenicity when two doses are given. We compared a new Triton X-100 SPV (Connaught Laboratories, Inc.) with the commercially available Tween-ether SPV (Parke-Davis & Co.) in 76 children and young adults 2 to 25 years old; there were 39 and 37, respectively, in each vaccine group. Both vaccines contained influenza A/Brazil/78, A/Texas/77, and B/Hong Kong/72 (7 microgram of hemagglutinin for each strain); two doses were administered 1 month apart. Among persons seronegative by the hemagglutination inhibition test, the geometric mean antibody titers rose to approximately 100 after the first

vaccination for influenza A/Brazil/78 and A/Texas/77. For B/Hong Kong/72, however, seronegative recipients developed lower geometric mean titers of approximately 32 after one immunization. Against the new B/Singapore/79 strain neither SPV stimulated adequate cross-reacting hemagglutination inhibition antibody (geometric mean titers of approximately 10). In conclusion, the new Triton X-100 SPV appears to be comparable to the ether-treated SPV in primed subjects. Further studies in unprimed children should be done to confirm this impression. In addition, it would be advisable to study other dosage regimens in unprimed children with these SPVs.

CT Check Tags: Comparative Study; Human; Support, U.S. Gov't, P.H.S.
Adolescent
*Antibodies, Viral: BI, biosynthesis
Child
Child, Preschool
Clinical Trials
Double-Blind Method
Ether, Ethyl
Hemagglutinins, Viral: AN, analysis
Infant
*Influenza A Virus, Human: IM, immunology
***Influenza Vaccine: IM, immunology**
Octoxynol
*Orthomyxoviridae: IM, immunology
Polyethylene Glycols
Polysorbates
Vaccination

L26 ANSWER 23 OF 32 MEDLINE on STN DUPLICATE 4
AN 82013204 MEDLINE
DN 82013204 PubMed ID: 6268957
TI Use of the enzyme-linked immunosorbent assay (ELISA) for the estimation of serum antibodies in an influenza virus vaccine study.
AU Jennings R; Smith T; Potter C W
SO MEDICAL MICROBIOLOGY AND IMMUNOLOGY, (1981) 169 (4) 247-58.
Journal code: 0314524. ISSN: 0300-8584.
CY GERMANY, WEST: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198111
ED Entered STN: 19900316
Last Updated on STN: 19900316
Entered Medline: 19811118
AB The value of the enzyme-linked immunosorbent assay (ELISA) for determining the serum antibody responses of volunteers following immunisation with various inactivated influenza virus vaccines was assessed, and the incidence of seroconversions, as measured by both haemagglutination-inhibition (HI) and ELISA response of the volunteers determined. ELISA was found to be more sensitive than the HI test in detecting serum antibodies, but was also less specific under the conditions used. With regard to efficacy, the whole virus vaccine proved to be more effective in inducing serum antibody in an unprimed population than either tween-ether **split** or subunit adsorbed vaccines, but the reverse situation held when the population was primed with respect to the antigen concerned.
CT Check Tags: Comparative Study; Female; Human; Male
Adolescent
Adult
*Antibodies, Viral: AN, analysis
Detergents: PD, pharmacology

*Enzyme-Linked Immunosorbent Assay
Hemagglutination Inhibition Tests
*Immunoenzyme Techniques
***Influenza Vaccine: IM, immunology**
Nonoxynol
Orthomyxoviridae: DE, drug effects
*Orthomyxoviridae: IM, immunology
Polyethylene Glycols: PD, pharmacology
Polysorbates: PD, pharmacology
Propiolactone: PD, pharmacology

L26 ANSWER 24 OF 32 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 1981:281772 BIOSIS
DN PREV198172066756; BA72:66756
TI REACTOGENICITY AND SEROLOGICAL RESPONSE TO POLYVALENT AQUEOUS AND ALUMINUM HYDROXIDE ADSORBED **TWEEN** ETHER **SPLIT** PRODUCT **INFLUENZA VACCINE** IN YOUNG ADULTS 1979.
AU GERTH H-J [Reprint author]; MOK-HSU Y CH
CS ABT FUER MED VIROL UND EPIDEMIOL DER VIRUSKRANKHEITEN, SILCHERSTR 7, D-7400 TUEBINGEN
SO Infection, (1981) Vol. 9, No. 2, pp. 85-90.
CODEN: IFTNAL. ISSN: 0300-8126.
DT Article
FS BA
LA ENGLISH
AB A comparative clinical trial with an Al(OH)3 adsorbed polyvalent **Tween**-ether **split** influenza vaccine and a **Tween** -ether **split** fluid vaccine of equal antigenic content was performed in young adults in 1979. Two vaccinations were given 28 days apart. Reactogenicity was evaluated using a questionnaire and the antibody response by the hemagglutination inhibition test (HI). The anti-N1-neuraminidase response was determined by the inhibition (NI) test in some of those who were vaccinated. Although reactogenicity was low, were significantly more local reactions reported from those receiving Al(OH)3 adsorbed vaccines. Prior to vaccination .apprx. 90% of the volunteer's antibody titers to A/Brazil/11/78, the H1N1 strain contained in the vaccine, were < 32. More than 50% of the volunteers with low titered antibody born after 1955 responded with a booster reaction to H1N1. NI tests were a much more sensitive indicator of priming. The antibody response in the primed individuals was highly satisfactory after 1 vaccination and there was no difference between the 2 vaccine types. In non-primed subjects 2 injections were necessary to reach a titer of ≥ 32 in .apprx. 80% of the volunteers for A/Brazil/11/78. There was no difference in the response to the 2 types of vaccine. The results of these and other studies show that it is not warranted to use Al adsorbed influenza vaccines.
IT Major Concepts
Immune System (Chemical Coordination and Homeostasis); Infection; Metabolism; Pharmacology; Toxicology

L26 ANSWER 25 OF 32 MEDLINE on STN
AN 79237295 MEDLINE
DN 79237295 PubMed ID: 467803
TI Isolation of biologically active components from rabies and other envelope viruses.
AU van der Marel P; van Wezel A L
SO DEVELOPMENTS IN BIOLOGICAL STANDARDIZATION, (1979) 42 93-8.
Journal code: 0427140. ISSN: 0301-5149.
CY Switzerland
DT Journal; Article; (JOURNAL ARTICLE)

LA English
FS Priority Journals
EM 197910
ED Entered STN: 19900315
Last Updated on STN: 19970203
Entered Medline: 19791026
AB Most human virus vaccines contain complete virus particles, either inactivated or attenuated. Besides components responsible for induction of neutralizing antibodies, other virus components (e.g. nucleic acids, lipids) are also administered upon vaccination. For envelope viruses the (glyco) proteins of the viral envelope are generally involved in the induction of neutralizing antibodies. Our investigations are focussed on the large scale preparation of these components from several viruses or virus vaccines, such as rabies and influenza. For virus disintegration we have tested several ionic anc nonionic detergents. Triton X-100 gave good results. Separation of solubilized components from the remainder of the virus has been carried out on a small scale by ultracentrifugation. For the purification of influenza hemagglutinin and neuraminidase we also used gelfiltration with success. The latter process can be scaled up easily. The main problem in the process of virus subunit preparation is the removal of detergent.
CT *Hemagglutinins, Viral: IP, isolation & purification
***Influenza A Virus, Human: AN, analysis**
Influenza A Virus, Human: DE, drug effects
Influenza Vaccine
*Neuraminidase: IP, isolation & purification
Rabies Vaccines
*Rabies virus: AN, analysis
Rabies virus: DE, drug effects
Surface-Active Agents: PD, pharmacology
Vaccines, Attenuated

L26 ANSWER 26 OF 32 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 1979:251330 BIOSIS
DN PREV197968053834; BA68:53834
TI THE SPECIFICITY OF THE ANTI HEM AGGLUTININ ANTIBODY RESPONSE INDUCED IN MAN BY INACTIVATED **INFLUENZA VACCINES** AND BY NATURAL INFECTION.
AU OXFORD J S [Reprint author]; SCHILD G C; POTTER C W; JENNINGS R
CS DIV VIROL, NATL INST BIOL STAND CONTROL, HOLLY HILL, HAMPSTEAD, LONDON NW3 6RB, ENGL, UK
SO Journal of Hygiene, (1979) Vol. 82, No. 1, pp. 51-62.
CODEN: JOHYAY. ISSN: 0022-1724.
DT Article
FS BA
LA ENGLISH
AB The anti-hemagglutinin antibody [Ab] response in adult human volunteers to inactivated whole virus or **tween** ether **split** influenza A/Victoria/75 (H3N2) and A/Scotland/74 (H3N2) virus vaccines was investigated using Ab absorption and single-radial-hemolysis (SRH) techniques. The concentrations of hemagglutinin (HA), nucleoprotein (NP) and matrix (M) antigens [Ag] measured by single radial diffusion (SRD) and rocket immunoelectrophoresis were similar for the whole virus and **split** vaccines. Whole virus and **split** vaccines induced cross-reactive (CR) Ab in 87% of vaccinees. Strain specific (SS) Ab to A/Hong Kong/1/68 or the homologous virus was induced less frequently than CR Ab. Higher anti-hemagglutinin Ab titers were detected in persons receiving the **split** virus vaccines than in those receiving the whole virus vaccines. No Ab to the type-specific matrix protein was detectable, but 33% of volunteers developed an Ab rise to type-specific

nucleoprotein Ag. The specificity of the anti-hemagglutinin Ab response in human adults to natural infection with A/Port Chalmers/73 (H3N2) virus was similar to that induced by inactivated vaccines in that a high proportion of subjects developed CR anti-hemagglutinin Ab, which reacted with A/Hong Kong/68 virus and the homologous A/Port Chalmers/73 virus and SS Ab for A/Hong Kong/68 virus. SS Ab for A/Port Chalmers/73 virus was infrequently stimulated by natural infection.

IT Major Concepts
Immune System (Chemical Coordination and Homeostasis); Infection; Metabolism

L26 ANSWER 27 OF 32 MEDLINE on STN
AN 79049324 MEDLINE
DN 79049324 PubMed ID: 712115
TI Reactogenicity and immunogenicity of whole and ether-Tween-**split** influenza A virus vaccines in volunteers.
AU Jennings R; Clark A; Oxford J S; Hockley D J; Potter C W
SO JOURNAL OF INFECTIOUS DISEASES, (1978 Nov) 138 (5) 577-86.
Journal code: 0413675. ISSN: 0022-1899.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 197901
ED Entered STN: 19900314
Last Updated on STN: 19970203
Entered Medline: 19790126
AB Two separate, double-blind studies were carried out in volunteers to compare the reactogenicity of, and serum antibody responses to, whole or ether-Tween-**split** inactivated influenza virus vaccines. In both studies the ether-Tween-**split** vaccines induced a lower rate of reactions. The serum hemagglutination-inhibiting (HAI) antibody response of volunteers to the A/Scotland/74 component of the **split** vaccine used in the first study was significantly greater than that following inoculation of A/Scotland/74 whole-virus vaccine. The neuraminidase-inhibiting (NI) antibody responses of the volunteers to each vaccine were similar. In the second study, a markedly better NI antibody response to the influenza A virus component was seen following immunization with **split**-virus vaccine, but the HAI antibody response to both **split** and whole vaccines was the same. In both studies the serum HAI antibody responses to the B/Hong Kong/73 component of the vaccines were similar. Challenge of the volunteers with attenuated influenza viruses homologous to the influenza A component of the vaccines showed both types of vaccines to be protective.
CT Check Tags: Case Report; Female; Human; Male
Antibodies, Viral: AN, analysis
Double-Blind Method
Hemagglutination Inhibition Tests
*Immunity
Influenza A Virus, Human: EN, enzymology
Influenza A Virus, Human: IM, immunology
Influenza Vaccine: AE, adverse effects
***Influenza Vaccine: IM, immunology**
Neuraminidase: IM, immunology
Placebos
Polysorbates

L26 ANSWER 28 OF 32 MEDLINE on STN
AN 78107569 MEDLINE
DN 78107569 PubMed ID: 604115

TI The antibody response and immunity to challenge infection induced by whole, inactivated and tween-ether **split** influenza vaccines.
AU Potter C W; Jennings R; Clark A
SO DEVELOPMENTS IN BIOLOGICAL STANDARDIZATION, (1977 Jun 1-3) 39 323-8. Journal code: 0427140. ISSN: 0301-5149.
CY Switzerland
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 197804
ED Entered STN: 19900314
Last Updated on STN: 19970203
Entered Medline: 19780417
CT Check Tags: Comparative Study; Human
*Antibodies, Viral
Antibody Formation
Ether, Ethyl
Hemagglutinins, Viral
*Influenza A virus: IM, immunology
***Influenza Vaccine**
Influenza Vaccine: AE, adverse effects
Neuraminidase: IM, immunology
Polysorbates
Vaccination: AE, adverse effects

L26 ANSWER 29 OF 32 MEDLINE on STN DUPLICATE 5
AN 75059621 MEDLINE
DN 75059621 PubMed ID: 4435958
TI Inactivated influenza vaccine efficacy: diminished antigenicity of **split**-product vaccines in mice.
AU Barry D W; Staton E; Mayner R E
SO INFECTION AND IMMUNITY, (1974 Dec) 10 (6) 1329-36. Journal code: 0246127. ISSN: 0019-9567.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 197502
ED Entered STN: 19900310
Last Updated on STN: 19900310
Entered Medline: 19750220
CT Check Tags: Animal; Male
Antibody Formation
*Antigens, Viral: AN, analysis
Chickens
Hemagglutination Inhibition Tests
Hemagglutination Tests
Immunization
***Influenza Vaccine**
Mice
Neuraminidase
Orthomyxoviridae: IM, immunology
***Polysorbates: PD, pharmacology**
***Surface-Active Agents: PD, pharmacology**
***Vaccines, Attenuated**
Vibrio cholerae: EN, enzymology

L26 ANSWER 30 OF 32 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 1974:143587 BIOSIS
DN PREV197457043287; BA57:43287

TI ANTIBODY RESPONSE OF HAMSTERS TO **INFLUENZA** A-2-HONG-KONG VIRUS **VACCINE** AFTER PRIMING BY HETEROTYPIC VIRUS INFECTION.
AU POTTER C W; JENNINGS R; REES R C; MCLAREN C
SO Infection and Immunity, (1973) Vol. 8, No. 2, pp. 137-144.
CODEN: INFIBR. ISSN: 0019-9567.
DT Article
FS BA
LA Unavailable
IT Major Concepts
Blood and Lymphatics (Transport and Circulation); Immune System (Chemical Coordination and Homeostasis); Infection; Metabolism

L26 ANSWER 31 OF 32 MEDLINE on STN
AN 73006448 MEDLINE
DN 73006448 PubMed ID: 4506997
TI Antibody responses and resistance to challenge in volunteers vaccinated with live attenuated, detergent **split** and oil adjuvant A2-Hong Kong-68 (H 3 N 2) influenza vaccines. A report to the Medical Research Council Committee on Influenza and other Respiratory Virus Vaccines.
AU Freestone D S; Hamilton-Smith S; Schild G C; Buckland R; Chinn S; Tyrrell D A
SO JOURNAL OF HYGIENE, (1972 Sep) 70 (3) 531-43.
Journal code: 0375374. ISSN: 0022-1724.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 197211
ED Entered STN: 19900310
Last Updated on STN: 19970203
Entered Medline: 19721116
CT Check Tags: Female; Human; Male
Adjuvants, Immunologic
Adult
Antibodies
*Antibody Formation
Detergents
Hemagglutination Inhibition Tests
*Immunity
*Influenza: PC, prevention & control
***Influenza Vaccine**
Neuraminidase
Neutralization Tests
Nose
Orthomyxoviridae: IM, immunology
*Vaccination

L26 ANSWER 32 OF 32 MEDLINE on STN
AN 70156070 MEDLINE
DN 70156070 PubMed ID: 5379936
TI Some aspects on the preparation of vaccines containing purified antigens.
AU Norrby E
SO PROGRESS IN IMMUNOBIOLOGICAL STANDARDIZATION, (1969) 3 159-64.
Journal code: 0427362. ISSN: 0079-6344.
CY Switzerland
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 197005
ED Entered STN: 19900101

Last Updated on STN: 19900101
Entered Medline: 19700520
CT Check Tags: Animal
*Adenoviridae: IM, immunology
Antibody Formation
*Antigens: IP, isolation & purification
Centrifugation, Zonal
Dogs
Ethers: PD, pharmacology
Hexamethonium Compounds: PD, pharmacology
Kidney
*Measles virus: IM, immunology
Nucleoproteins
***Orthomyxoviridae: IM, immunology**
Surface-Active Agents: PD, pharmacology
Tissue Culture
***Viral Vaccines**

=>